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DERMATOLOGY

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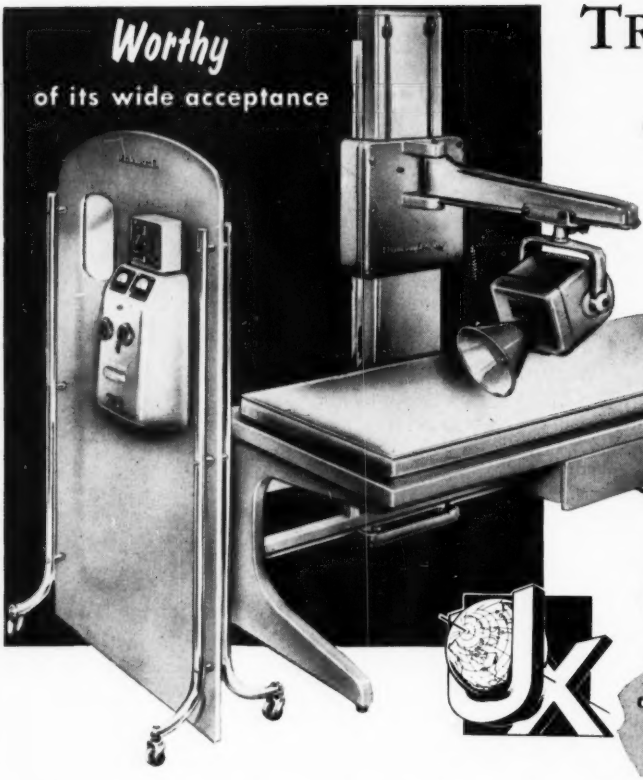

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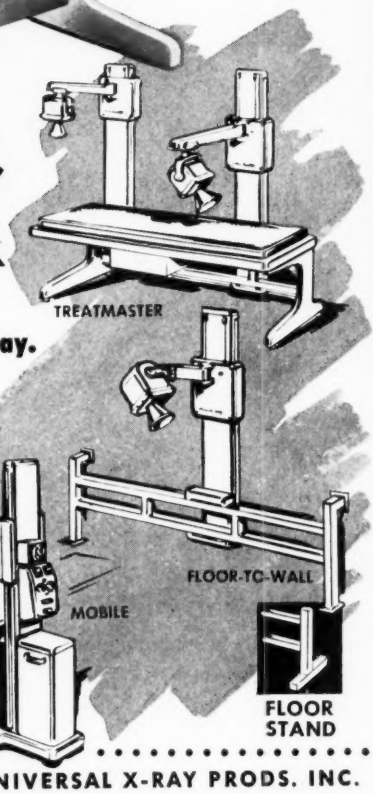

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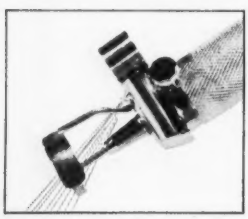

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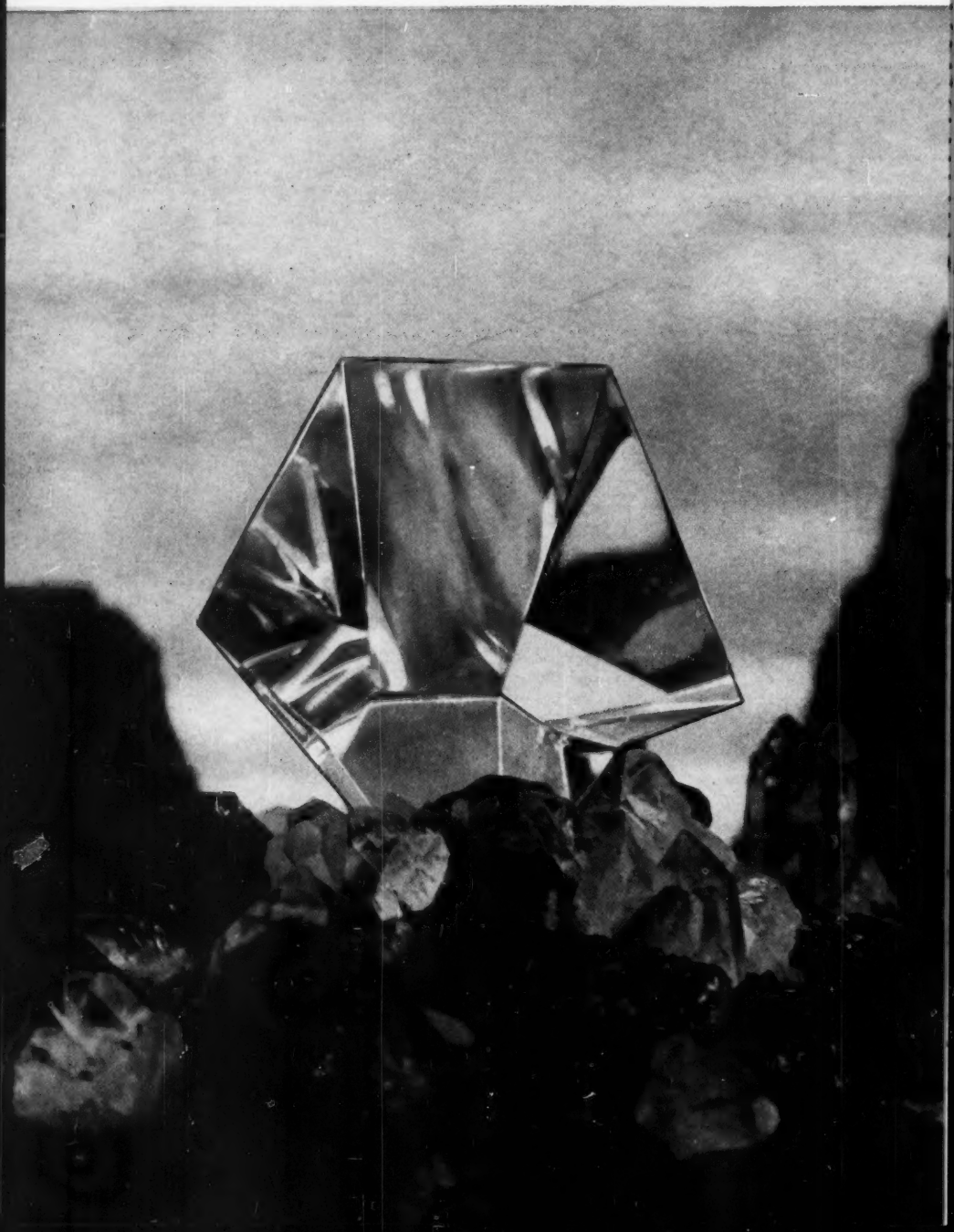

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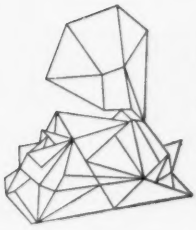

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References: (1) Gould, A. H. and Long, D. L.: Clinical Pharmacology and Therapeutic Use of Dexbrompheniramine Maleate (Disomer), a new Histamine Antagonist (submitted for publication). (2) Medical Department, White Laboratories, Inc.

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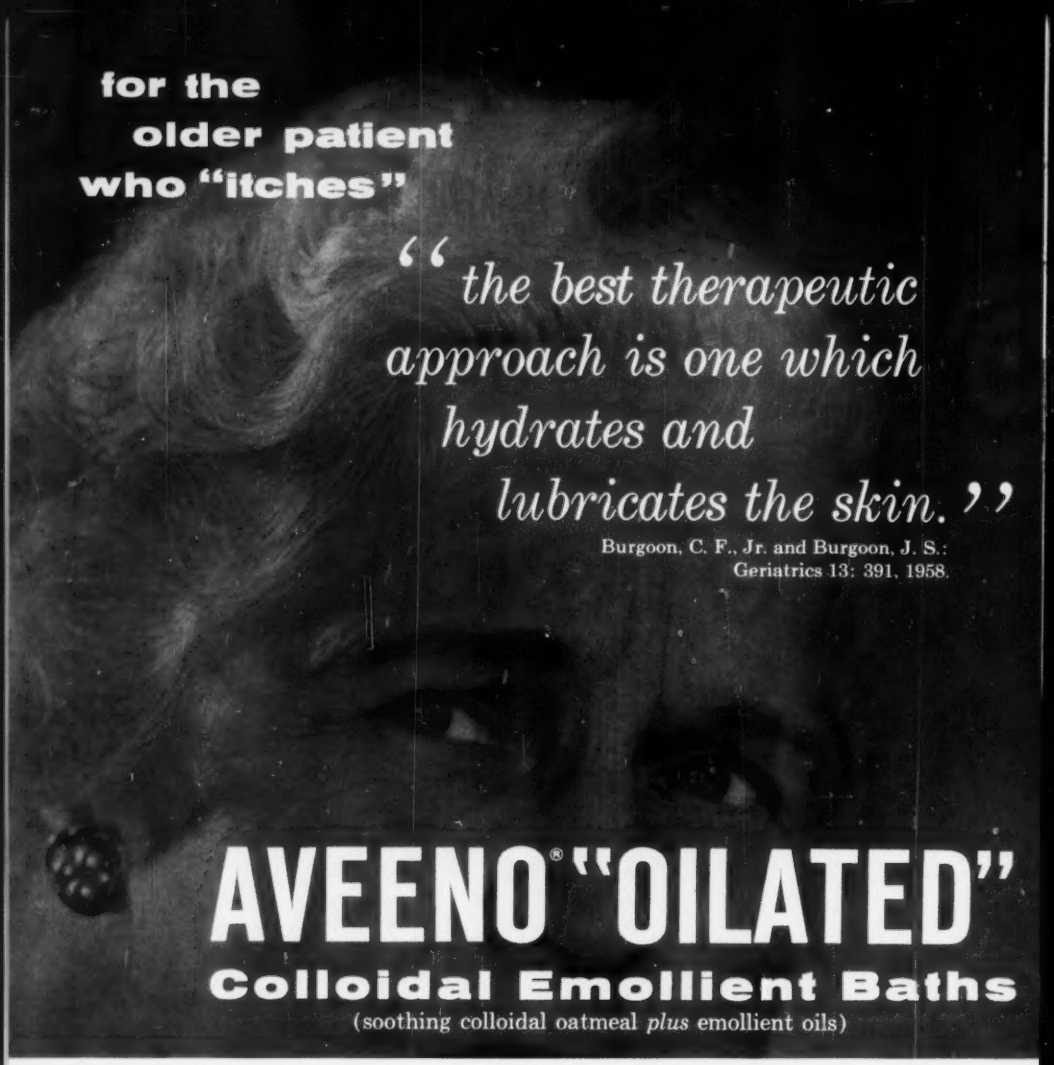
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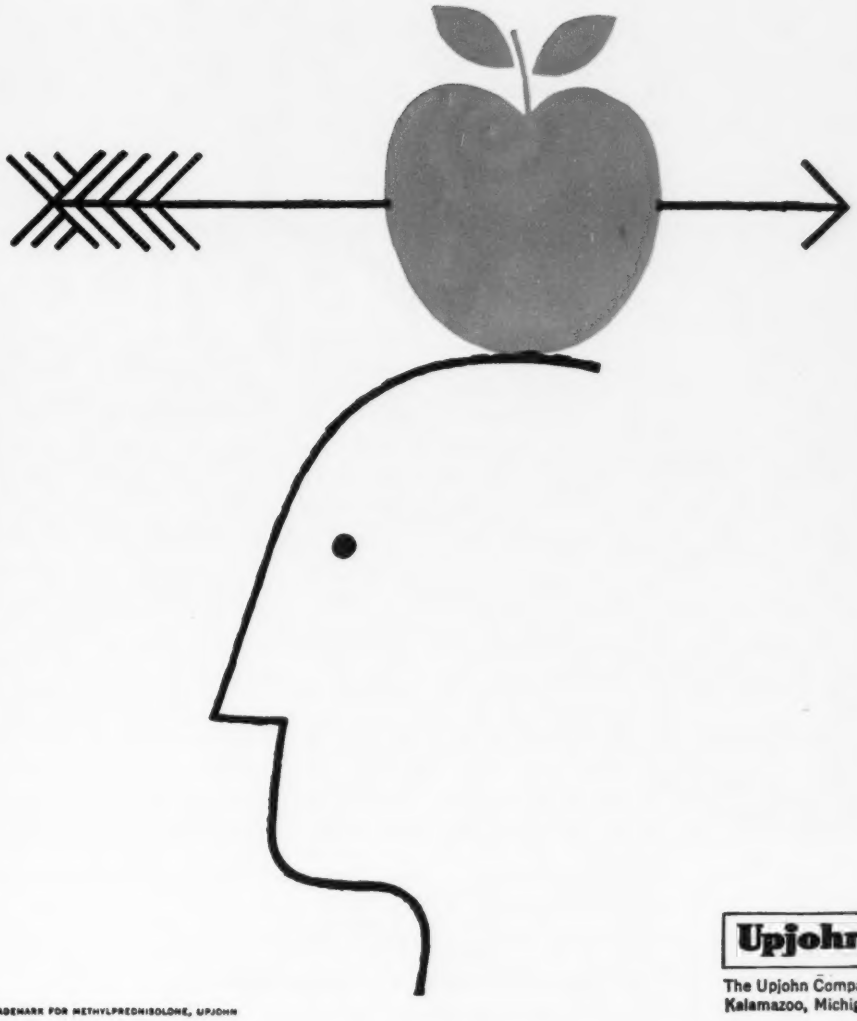

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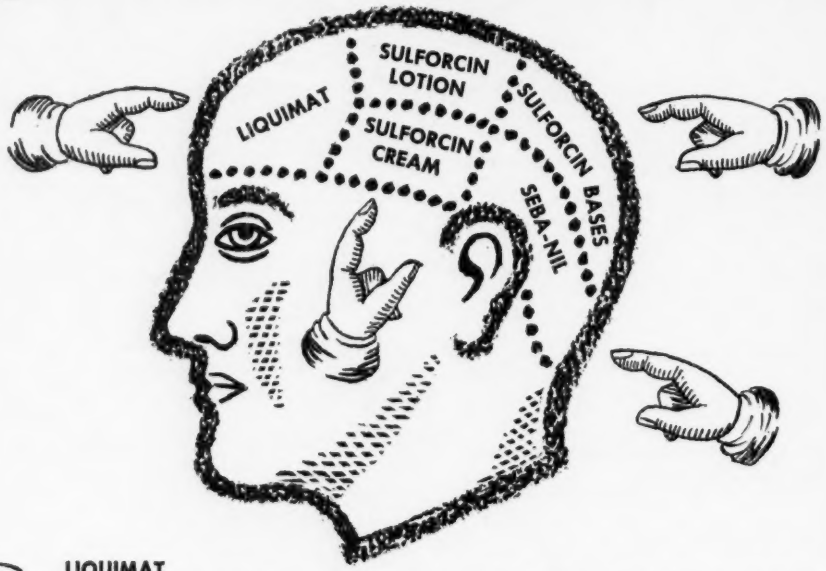

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In cartons of 12 packets. (Each packet contains 2.3 gm. of powder, for preparation of 8 fluid ounces of solution containing 1% sodium propionate and 0.0025% water-soluble chlorophyllin.) Also in 4-ounce and 16-ounce jars.

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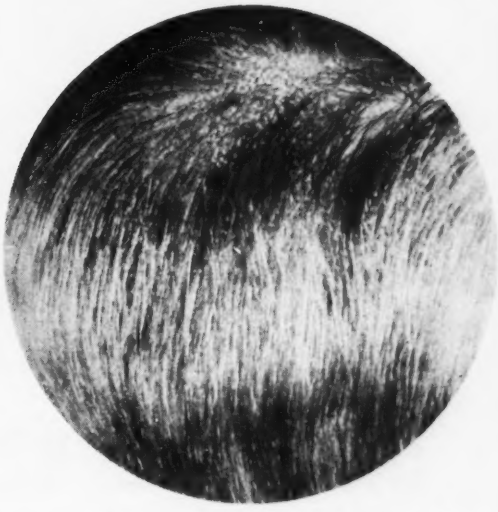
clears the tineas from head to toe– orally

new **fulvicin**
griseofulvin
Schering

In tinea capitis

Before FULVICIN: Tinea capitis *(Microsporum audouini)* in a 7-year-old boy.



After FULVICIN: Normal, new hair growth after 6 weeks of oral therapy.

Photos courtesy of M. M. Nierman, M.D., Calumet City, Ill.

Lesions clear, cultures become negative in

tinea corporis: 4 to 5 weeks[1]
tinea cruris: 4 to 6 weeks[1]
onychomycosis: 4 to 6 months[1]
tinea pedis: 6 to 8 weeks[1]

first *oral* fungistat to penetrate keratin *from the inside*... acts to check invading ringworm fungi *(Microsporum, Trichophyton, Epidermophyton)*...usually well tolerated, side effects rare in therapeutic doses.

For complete information about dosage, indications and precautions consult Schering Statement of Directions.

Packaging: FULVICIN Tablets, 250 mg., bottles of 30 and 100.

1. Robinson, H. M., Jr., *et al.*: Griseofulvin, Clinical and Experimental Studies, A.M.A. Arch. Dermat., in press.

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Maltbie Laboratories Division / Wallace & Tiernan Incorporated, Belleville 9, N. J.

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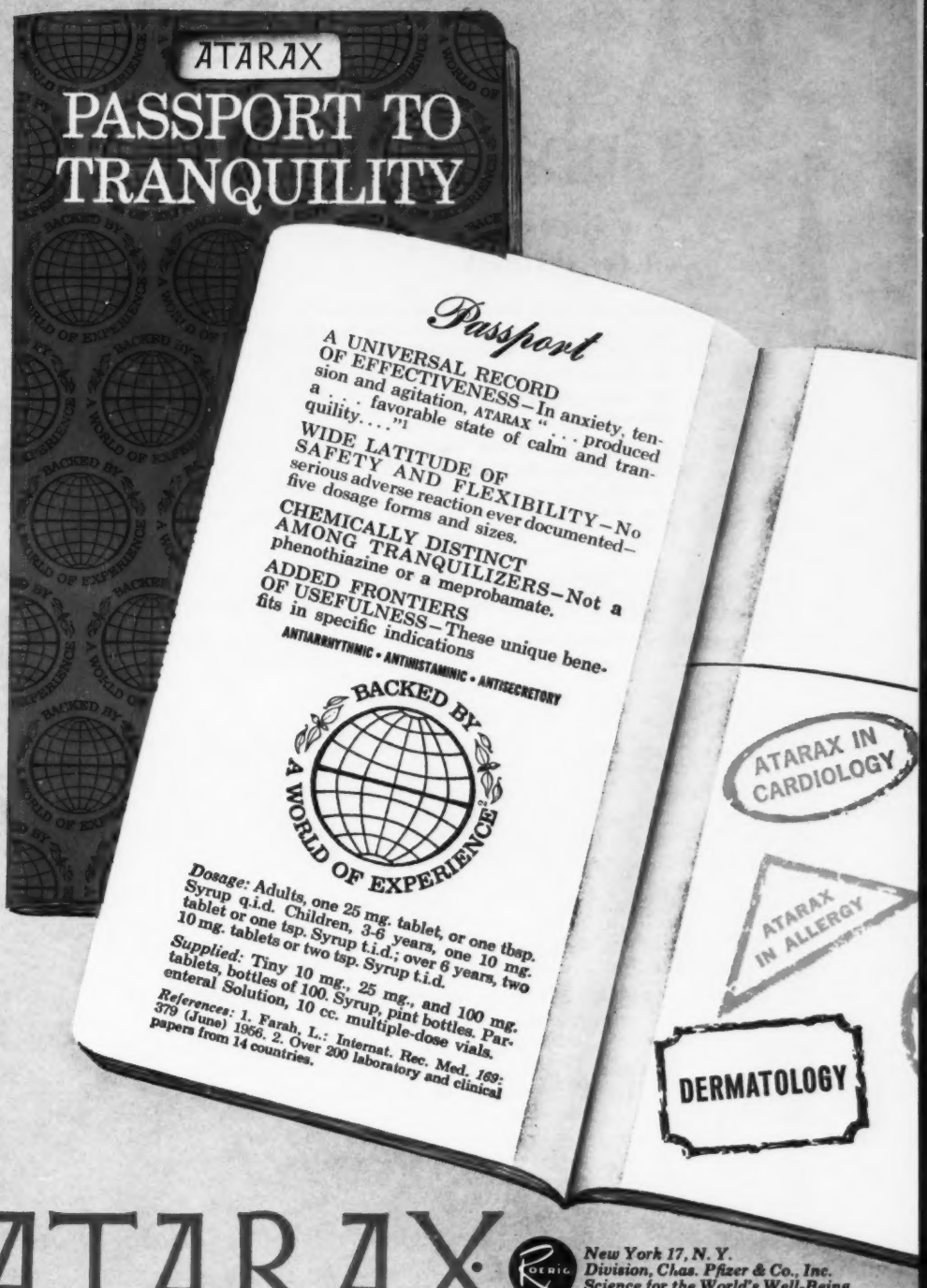
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Supplied: Tiny 10 mg., 25 mg., and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.
References: 1. Farah, L.: Internat. Rec. Med. 169: 379 (June) 1956. 2. Over 200 laboratory and clinical papers from 14 countries.
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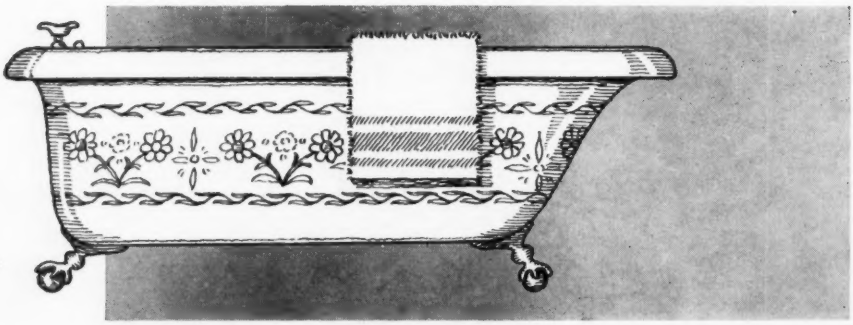

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1. Pillsbury, D. M., Shelley, W. B., and Kligman, A. M.: Dermatology. Philadelphia, Saunders, 1956. P. 733.
2. Goldman, L., and Preston, R. H.: A.M.A. Arch. Derm., 80:222 (Aug.) 1959.

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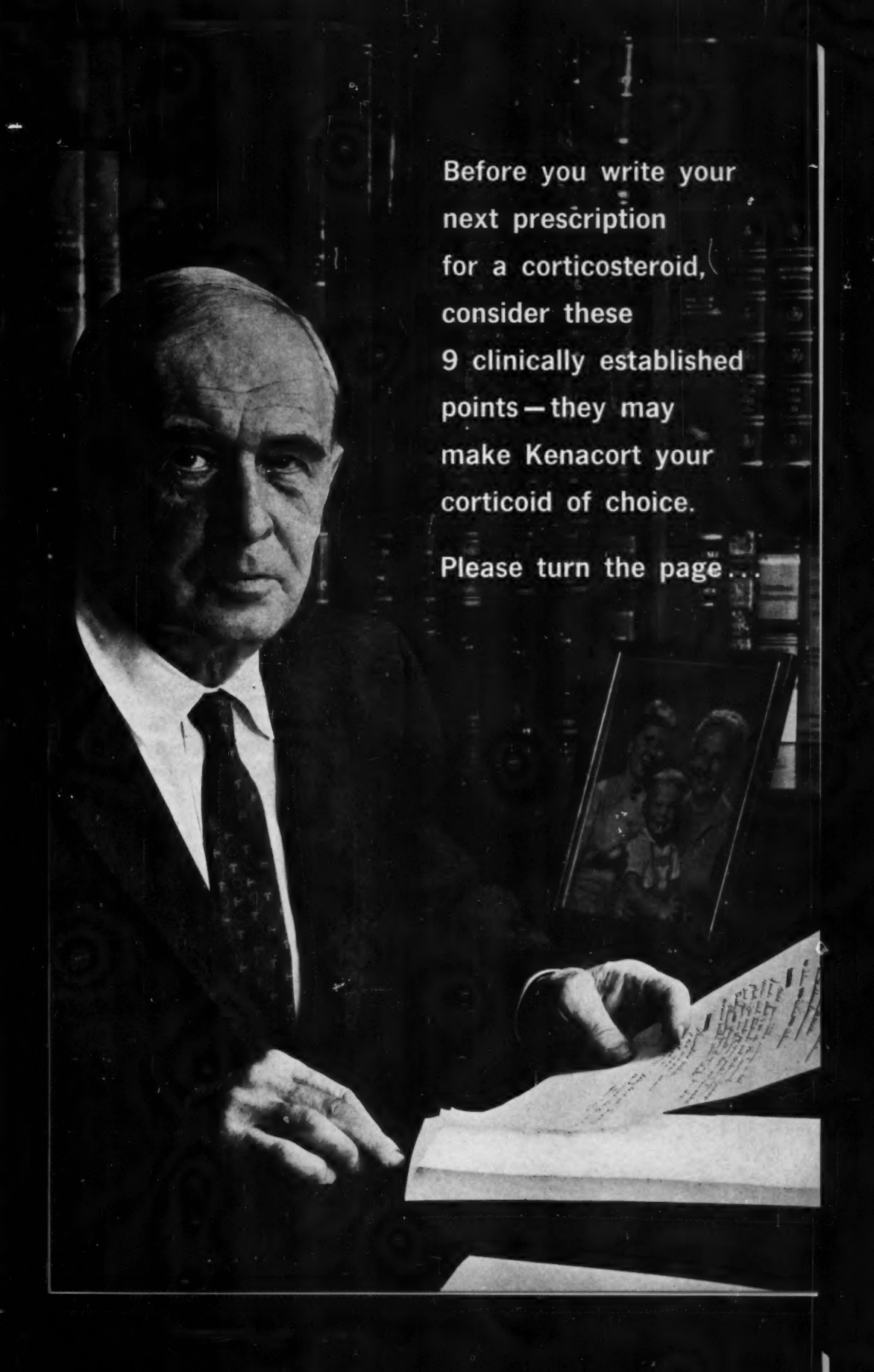
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Allison, J. R., Sr., and Allison, J. R., Jr.: Monographs on Therapy 3:99 (Oct.) 1958.

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Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.: J. A. M. A. 167:58 (May 3) 1958.

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no sodium or water retention—low salt diet not necessary

Hartung, E. F.: J. A. M. A. 167:973 (June 21) 1958.

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Council on Drugs: J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number **5**

less likely to create electrolyte disturbance

Bongiovanni, A. M.; Mellman, W. J., and Eberlein, W. R.: J. Pediat. 53:3 (July) 1958.

pre-prescription point number **6**

no secondary hypertension—no significant change in pulse, respiration, or blood pressure

Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J. A. M. A. 167:959 (June 21) 1958.

Bernsten, C. A., Jr., and others: New York Rheumatism Association, Annual Meeting, New York, April 9, 1959.

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J. A. M. A. 169:257 (Jan. 17) 1959.

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Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
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J. A. M. A. 169:257 (Jan. 17) 1959.

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Hartung, E. F.:
J. A. M. A. 167:973 (June 21) 1958.

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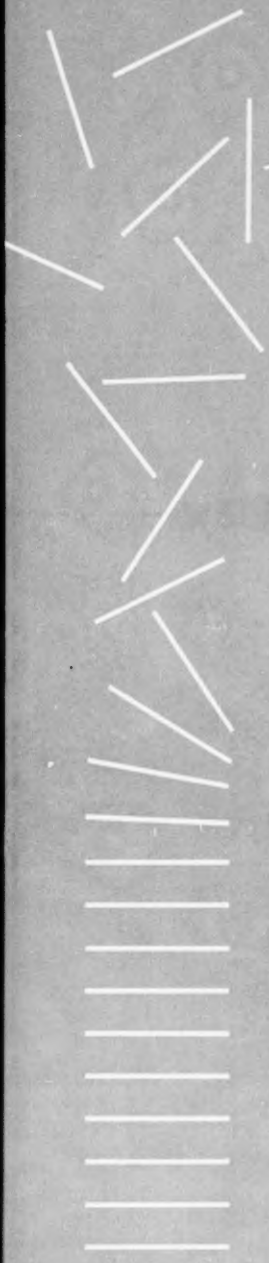

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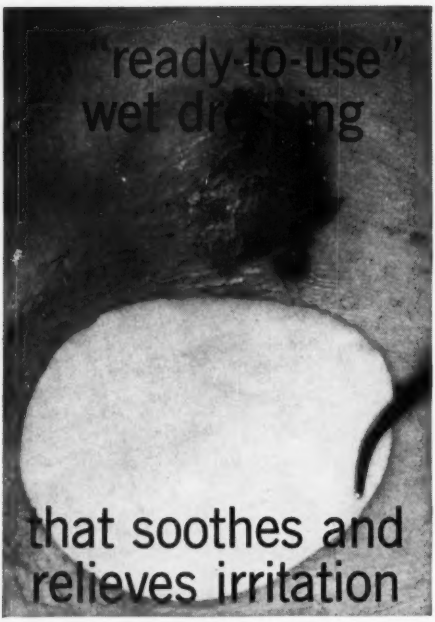

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*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

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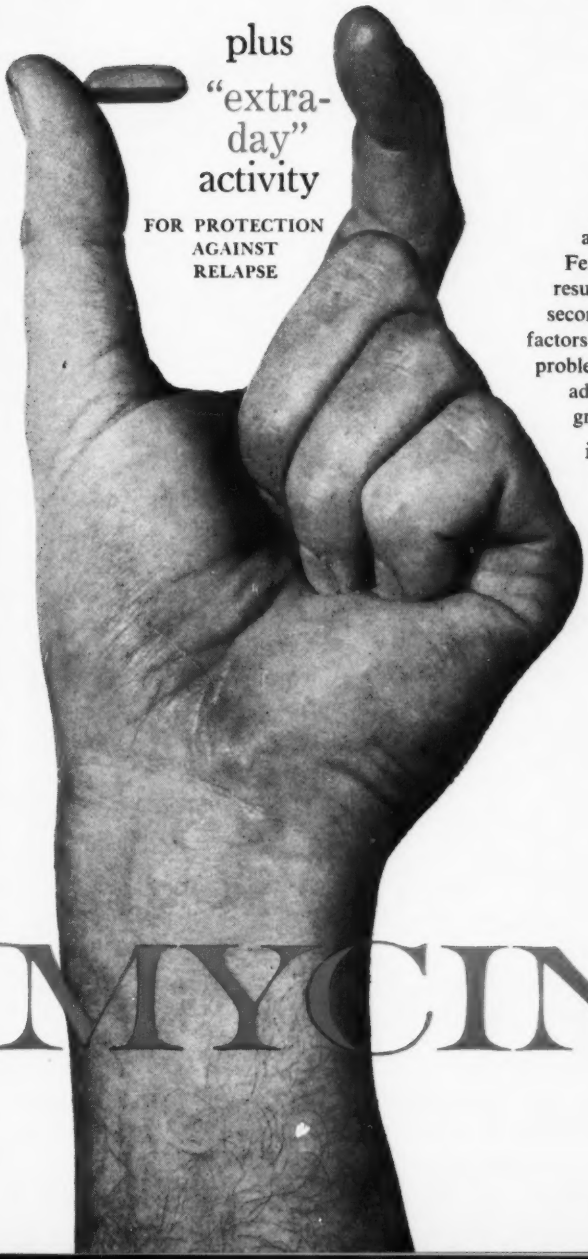

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1. Saperstein, R. B.: Presented at 107th annual meeting of American Medical Assn., San Francisco, Calif., June 23-27. 1958.

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A.M.A. ARCHIVES OF
DERMATOLOGY

Contributions by Dermatology to the Progress of Medicine

J. LAMAR CALLAWAY, M.D., Durham, N.C.

This attempt at listing some fundamental contributions by dermatologists and dermatologic laboratories to the progress of medicine generally, is made to point up the influence of dermatology as a scientific specialty that it is. This admittedly incomplete survey will unquestionably do a grave injustice to many noteworthy contributors. Had I not committed myself to this task of compiling data and had I not received helpful suggestions from many of you, I should long ago have abandoned the idea.

However, I feel so strongly that dermatology and dermatologists have, on occasion, been unjustly maligned and not given proper recognition that this effort seems justified. Errors of omission and errors of commission may be numerous, but none will be intentional.

Recognizing the inadequacy of a personal and somewhat prejudiced evaluation of what may constitute a real or significant contribution, this summary is an attempt to catalogue what may be called "advances," but, as Michelson has pointed out, in all likelihood they should more properly be referred to as "additions" to our knowledge. The character of dermatology has undergone radical change.

Dermatology today might more concisely be described as "cutaneous medicine." Although the morphologic characteristics of cutaneous lesions, readily visible to the naked eye, often offer a practical solution to the problem, the dermatologist's concept is never limited to the integument and often involves the evaluation of bone marrow, lymph nodes, endocrine glands, various immunologic studies, biochemical analyses, as well as scrapings, cultures, and biopsies of the skin. Curtis, Sutton Jr., O'Leary, Stokes, and many others have for years stressed the importance of the whole individual and not skin alone. Today the dermatologist needs and, indeed, has a background as profound as the internist.

Dermatologists are increasingly becoming more active in medical education, participating in clinical pathological conferences, actively engaging in hospital "grand rounds," and during the past three or four years several professors of dermatology have visited other medical schools where they were visiting professors of medicine for a period. All of these activities have contributed to advancement of our specialty and a better interrelationship with the various departments.

Recently, at one time on the dermatology service at Duke University Medical Center, the following problems were under

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investigation. One problem under study involved a patient who had a sclerodermatous problem in which the evaluation necessitated the service of the peripheral vascular surgeon to evaluate the Raynaud's possibility, the radiologist for recumbent barium-swallow studies, the rheumatologist to determine if the primary problem was one of rheumatoid arthritis, not to mention skin and muscle biopsy, blood chemistry evaluations, and other studies. Incidentally, the patient also had a profound anemia and an acoustic neuroma.

Among other "dermatologic" problems in the hospital at this time were patients with dermatomyositis, systemic lupus erythematosus, erythema induratum, sporotrichosis, ophthalmic herpes zoster, delusions of parasitosis, neurodermatitis, and contact dermatitis with autosensitization.

In an effort to solve these problems virtually every service in the hospital was part of the evaluating team. The biochemist, psychiatrist, otolaryngologist, pathologist, internist, mycologist, and others were integral participants in the study. This discussion has presented many problems to me. Can Parks-Weber be considered a dermatologist? Many of his contributions are in the dermatologic field. If he is in reality a dermatologist, the syndromes of which he is a part, such as Rendu-Osler-Weber, Sturge-Weber-Kalischer, Weber-Cockayne, and Weber-Christian's disease should be a part of this review.

It may be remembered that many dermatologic conditions were described by nondermatologists. Urticaria pigmentosa was described by an ophthalmologist; epidermolysis bullosa was described by a neurologist; and sporotrichosis was described by a medical student, who later became a gynecologist. So-called "firsts" are difficult. Despite an attempt to list the author first responsible for a discovery, literature reviewed can be confusing and erroneous.

Descriptions by dermatologists, such as those dermatoses described by the elder Jadassohn, of what may be considered purely "dermatologic" conditions—for example, cutis verticis gyrata, granulosis rubra nasi, pachyonychia congenita, and similar primary dermatologic conditions described by other dermatologists, will not be considered in this treatise.

The subdivisions used in this discussion are arbitrary, and there may be disagreement with the various classifications employed. Should infectious eczematoid dermatitis be considered under the section on bacteriology or should it more properly be considered under the section on immunology? Should nodular vascularis be considered under the vascular category or as one of the "collagen diseases?" Is erythema nodosum as first described by Willan a dermatologic entity, or, is this condition merely a symptom complex of various organ or system disease? If the answer to this question was unequivocal, the assembling data for this report would have been simplified. Telegraphic statements will be used to reduce the volume of this report, which in turn may give it the sound of a telephone directory.

Bacteriology—Microbiology

Dermatologists have made notable contributions in the field of bacteriology. Unna and Ducrey first demonstrated the organism responsible for chancroid and Pacheco first described dermato-brucellosis. Hebra and Kaposi described and isolated the organism responsible for rhinoscleroma (respiratory scleroma). Neisser discovered, isolated, and identified the gonococcus as being the cause of gonorrhea, and among Neisser's other contributions was the first bacterial study of cutaneous diphtheria. Hansen and Neisser first stained the acid-fast organism causing leprosy. Buschke was co-discoverer of the organism of cryptococcosis and Montenegro developed the intradermal skin test for the diagnosis of South American leishmaniasis. Ramos e Silva is responsible for much of our knowledge of pinta as a result of his clinical and experimental studies. The etiologic agent for pinta was first

isolated in Mexico by Blanco and named Treponema herrejon, although Brumpt visited Mexico, obtained slides and material, returned to Europe and published his material before Blanco under the name of Treponema carateum. Grav and Alfonza independently isolated the Treponema carateum. Engman Sr. described infectious eczematoid dermatitis, showing the peculiar allergic-immunologic response of the skin to certain pyogenic infections. Hopkins studied the influence of staphylococci and streptococci on the skin in relation to their inherent dangers from absorption of toxins. Callaway and associates have shown that acute glomerular nephritis may develop when chronic pyogenic infections of the skin are neglected. More recently, a comprehensive study of the normal and abnormal host-parasite relationship between the skin and its bacterial flora has been elucidated by Pillsbury, Kligman, Rabell, and associates. Mitchell-Hegg and C. T. Nelson have also contributed in this area. Although Hellerstrom did not isolate the Microbacterium balnei, he is responsible for the clinical recognition and description of the swimming pool granulomas as we know them. Olansky and colleagues have developed a technique for identifying the Hemophilus ducreyei organism bacteriologically. Dubini discovered and identified the Ancylostoma duodenale.

Virus Diseases

Contributions by dermatologists in the field of virus diseases include those of Jadassohn, who demonstrated the transmissibility of warts in man, Ciuffo, who first proved the filtrability of the virus of warts, and Lipschutz, who first demonstrated inclusion bodies in various virus infections of the skin, specifically herpes zoster and called attention to their specific significance. Brussgaard showed the direct relationship between the virus of varicella and the virus of herpes zoster, and Juliusberg demonstrated the transmissibility of molluscum contagiosum. Lipschutz was also the first to visualize the molluscum contagiosum virus. Grueter was one of the early workers who showed the transmissibility of herpes virus to experimental animals. Duhring in his textbook presented illustrations of multinucleated giant cells associated with virus diseases of the skin. Peterkin in England, and Wheeler and Cawley in this country, have discovered and isolated the etiologic agent in orf and are responsible for our understanding of the disease. Wile and Kingery were first to demonstrate the infectiousness of molluscum contagiosum, and Blank and his co-workers have demonstrated that the virus of cowpox and vaccina are different. Tzanck introduced the technique of a direct smear and immediate examination of stained film to demonstrate multinucleated giant cells for the diagnosis of virus diseases. Frei demonstrated that lymphogranuloma venereum is a separate venereal disease caused by a virus (this agent may actually belong in the rickettsia category) and further developed the Frei test for the diagnosis of lymphogranuloma venereum. Nicholas and Favre are responsible for our first clinical description of lymphogranuloma venereum and Grace was co-author of a complement-fixation test for this disease. Kaposi's explanation of the varicelliform eruption has stood the test of time. Wheeler has demonstrated in virus tissue culture work the mechanism of virus infection of man and in tissue culture. Blank and his colleagues have pioneered in the field of electron microscopy on the virus of zoster and simplex, and, further, Blank and his colleagues were among the first to grow skin on the chorioallantoic membrane (prepuce).

Educational Features

Hebra established the first separate hospital service and university lectureship for dermatology and made an effort to classify the various dermatoses pathologically. Willan and Bateman made an effort to classify dermatoses morphologically, whereas Alibert, Jadassohn and others contributed toward the recognition of dermatology

as a separate entity and gave it stature. Establishment of the American Board of Dermatology and Syphilology in 1932, one of the earliest Boards organized, further added to the recognition of dermatology as a scientific specialty. Training schools and services throughout the country, including the Philadelphia School, the New York Postgraduate School, the Mayo Clinic, the University of Michigan, the University of Illinois, St. Louis and other training centers well known to us all, have added immeasurably to our position in medicine. At least nine professors and heads of the department have been produced by the University of Michigan, Department of Dermatology, and also by the University of Pennsylvania, Department of Dermatology. Following Worcester's first textbook on dermatology in the United States, numerous dermatologists in this country and abroad have written textbooks on dermatology, syphilology, mycology, physiology, irradiation, pathology, and medically interrelated subjects all of which have given to dermatology its proper recognition and credits.

X-Irradiation Therapy

Dermatologists have performed their share of the work evaluating quality of x-rays, filtration studies, half-value layer, effect of indirect x-ray irradiation and proper x-ray therapy for various dermatoses, lymphomatous diseases, and malignant tumors. Pusey, Sequira, MacKee, Cippolaro, Besnier, Becquerel, Schiff, Keinbock, and Meischer were dermatologists who pioneered in the development of dosage schedules for the treatment of various dermatoses and lymphomas. Sabouraud developed the pastille for x-ray measurement. Freund first used epilation and Saboraud and Noire used epilation of the scalp as a treatment for tinea capitis. Hazen used the amount of x-ray therapy necessary to epilate mice as a biologic standard for x-ray dosage, and MacKee and Kingery developed an arithmetical computation and helped to put x-ray dosage on a mathematical basis. Belisaro and others developed the concept of the erythema dose in x-ray therapy. Cippolaro, MacKee, and Mutscheller worked on absorption studies and area factors, while Andrews has evaluated the exit dose. Baer, Borata, Sulzberger, and Pillsbury have attempted to evaluate the long-range effect of x-ray therapy and of particular interest has been the measurement of the gonadal dose of irradiation in routine dermatologic x-ray therapy. This was first measured by Callaway and his associates and subsequently by Andrews, Domonkos, Witten, Sulzberger, Stewart, and Alden.

Radium Therapy

Becquerel helped in separating and evaluating the alpha, beta, and gamma rays of radium. The "Becquerel burn" developed as a result of Becquerel's carrying a tube of radium in his waistcoat for several hours and first called our attention to the inherent dangers of irradiation. Besnier and Danlos in Europe, and Morrow, Shelmire, Fox, Taussig, Cole, Driver, Pipkin, Lehmann, Seale, and others are dermatologists who have contributed to our knowledge and use of radium in this country.

Thorium X and Isotopes.—The development and use of thorium X and the various radioactive isotopes becoming available to us are being evaluated and studied by many dermatologic centers.

Supersoft Irradiation

Supersoft irradiation, called Grenz or Bucky rays (infraroentgen) was first utilized by Schultz and Stern and later by MacKee, Kalz, and Eller. Pillsbury, Klem, Baer, and Witten have recently comprehensively reviewed the subject of Grenz irradiation.

Beta Rays

High energy electrons generated by some two and a half million volts and which have a biologic effective range limited to the first 7 to 10 mm. of tissue, have been studied by Fromer, using the monoenergetic elec-

tron beam from a Van deGraeff accelerator. This form of irradiation has been used primarily in mycosis fungoides and other lymphomatous diseases.

Light Therapy

A dermatologist, Tappeiner, first elucidated the photodynamic effect of light, and Finsen made physiologic studies of ultraviolet light irradiation, and further perfected the ultraviolet light, using it successfully in the treatment of many skin conditions, especially tuberculosis. Krohmayer developed the first water-cooled ultraviolet light for medical uses.

Biochemistry

Although many dermatologists have worked in the biochemical field and have, in the main, made liberal contributions to biochemistry in medicine generally, there are several outstanding contributions by dermatologists to what might be called the pure field of biochemistry. Schaaf, Bloch, and Wohler long ago recognized the labile state of the emulsion of lipids in sera of patients with certain xanthomas. Lever has demonstrated the presence of inhibitors of lipemia clearing activities in various lipemic states. Lerner first isolated and named the protein, cryoglobulin, and described the syndrome of cryoglobulinemia. In addition, Lerner demonstrated the mechanism in which the aromatic ring of tyrosine and phenylalanine break down in the body. Rothman, Smiljanic, Weitkamp, and Wheatley have identified and measured the fatty acids, alcohols, steroles, hydrocarbons, and vitamins in lipid surface film. L. Brunsting and associates have applied paper electrophoresis to dermatologic conditions and Flesch and Esoda are responsible for much of our knowledge of the biochemistry of the epidermis. Wheatley has isolated chemicals that are precursors of cholesterol in human tissue, and Urbach was the first to measure the glucose content of the skin. More recently Urbach, Lentz, Matsumato, Pillsbury, Kulchar, and Cornbleet have worked in the field of glucose metabolism of the skin. Weitkamp, Smiljanic, and Rothman demonstrated the existence of fatty acids with an odd number of carbon atoms. This may well be the first time that a purely dermatologic investigation has influenced the outlook of biochemistry.

Pigmentation

Bloch was the first dermatologist to make systematic studies of pigment metabolism and among his outstanding observations was that when a frozen section of human skin was incubated in a buffered solution of DOPA, melanocytes acquired an increased amount of pigment. Subsequent investigators considered the two enzymes, tyrosinase and DOPA-oxidase, to be necessary for pigment formation, but Fitzpatrick and Lerner showed that the two enzymic activities of tyrosinase and DOPA-oxidase belonged to a single complex. The first isolation of a melanocyte stimulating hormone (MSH) from the pituitary gland was accomplished by Lerner and his associates and among Lerner's other contributions is the recent work of Lerner, Case, and associates, in which the antiMSH factor, melatonin, has been isolated from the pineal gland. Unna, Pollitzer, and Curth are responsible for our recognition and understanding of acanthosis nigricans as a systemic disease. Meischer, Rothman, Becker, and Becker, Jr., Flesch, Traub, Shaffer and others have further increased our knowledge of the pigmentation problems, particularly the problems involving pigmented nevi, lentigo, and freckles.

Vitamin

J. Jadassohn described the first clinical signs of the dermatologic manifestations of pellagra, and Casal described the dermatitis of the neck (Casal's collar), and early gave us a better understanding of the dermatitis associated with pellagra as influenced by light. Frazier and Hu, and more recently Sullivan, have added to our knowledge of vitamin deficiency of the skin, and the con-

dition, Kwashiorkor, has recently been recognized in this country by Henington, Caroe, Derbes, and Kennedy.

Immunology—Allergy

In the field of immunology and allergy dermatologists have shared the progress made. An understanding of the incubation period, sensitization, cross sensitization, desensitization, localized sensitivity, chemical features associated with tissue, sera, and cell antibodies has been developed by Jadassohn, Bloch, Darier, Mayer, Frei, Haxthausen, Perutz, Sulzberger, Baer, Rostenburg, Cormia, and Kanof. J. Jadassohn developed the patch test for specific epidermal sensitivity and first recognized the mechanism of the development of trichophytids which was further evaluated by Williams. Tuberculous allergy and immunity was one of the more fertile investigative fields beginning with Darier's recognition of tuberculids and later studied by Lewandowsky, Kitamura, Martenstein, and Noll. Frei first sensitized animal skin to simple chemicals such as arsphenamine and later in the Jadassohn school, human skin was sensitized with salicylates followed by the more extensive experiments using substances such as dinitrochlorobenzine and related compounds. Whitfield recognized that autosensitization dermatitis was merely a part of the larger concept of autoimmune disease, and Bloch and Mazzini continued similar investigations with Trichophyton skin tests. The Prausnitz-Küstner and the Konegstein-Urbach passive transfer concepts opened the field of circulating antibodies to investigation. Urbach discovered that feeding specific food digests, propeptans, reduced or eliminated the dangers of anaphylactic shock. The work of Danbolt, Lomholt, Haxthausen, and Nelson in evaluating the Kveim reactions have added greatly to our knowledge of the immunologic process associated with sarcoidosis. The entire problem of eczematous sensitization has been made more understandable by the work of Baer, Sulzberger, Kanof, Epstein, Cormia, Peck, and Mayer. The concept of "skin memory" developed by Sulzberger, and the work of Rostenberg and Bluefarb, who demonstrated the pronounced depression of delayed types of allergenic reactions in the lymphoblastomas, have in a like manner contributed to the over-all knowledge of immune mechanisms. In the field of desensitization or hyposensitization Gougerot and Meyer first used Staphylococcus vaccines in resistant sycosis and other pyogenic infections. Kligman has reconstructed our concept of immunity in tinea capitis.

Mycology

In the field of mycology, contributions by dermatologists cannot be over emphasized. The original work of Gruby, Sabouraud's systematic classification of the dermatophytes, Majocchi's first recognition of the cutaneous lesions of actinomycosis, Buschke and Busse, who first recognized the causative organism of cryptococcosis (European blastomycosis), Lutz and Almeida isolated paracoccidioides brasiliensis and classified South American blastomycosis. Gilchrist recognized and described the organism causing North American blastomycosis and was also co-discoverer of the organism coccidioides immitis. Lane recognized and described the first case of chromoblastomycosis in North America. Ormsby was the first person to recognize the systemic nature of blastomycosis. Whitfield first recognized that so-called "athlete's foot" was due to superficial dermatophytes. The more recent recognition of acrodermatitis enteropathica by Danbolt and Closs is another dermatologic contribution to our over-all knowledge of fungus diseases. Who can overlook the contributions of Weidman, Pardo-Castello, Swartz, Hopkins, Lewis, Wilson, Curtis, Castellani, Lamb, and Blank in the field of superficial and deep mycoses and particularly in our knowledge of the immunology of the deep mycoses?

Syphilis

Our knowledge of the protean disease, syphilis, is largely the result of dermato-

logic investigation and study, beginning with Hoffman, who was co-discoverer of the motile organism causing syphilis, which they called the spirocheta pallida, later more correctly named the Treponema pallidum. The early observations of Ricord, the studies of Diday in hereditary syphilis, and Hutchinson's contribution of the "Hutchinson's triad" in prenatal syphilis, are well known accomplishments. Fournier recognized the importance of syphilis as a cause of degenerative disease, particularly tabes and paresis. Boeck, Brussgaard, and Danbolt have contributed to our knowledge concerning the fate of untreated syphilis, and Olansky and his associates have pursued a similar study on the results of untreated syphilis in the male Negro. The life cycle of the spirochete was studied by Ingraham and DeLamater. Among other important contributions was Beerman's recognition of arsphenamine-resistant spirochetes; the studies by Schoch and Alexander on relapse versus reinfection; Wile's studies on visceral syphilis and his description of the "therapeutic paradox"; the monumental contribution of the clinical cooperative group in which O'Leary, Stokes, Cole, and Wile were the dermatologists working with collected statistical data that produced a sound understanding of syphilis in relation to treatment, complications, reactions, and the natural course of the disease; Kemp's studies in the immunology of syphilis, as well as experimental syphilis studies by many contributing dermatologists, have added immeasurably to our understanding of the disease. Most of the treatment schedules for syphilis and much of the development in serologic testing for syphilis was developed by dermatologists. Chargin, Hyman, and Leifer reinstituted massive therapy (therapia sterilizans magna), the dream of the early syphilologists.

However, the outstanding contribution in the field of syphilis is probably the American discovery of the antitreponemal effectiveness of penicillin. The efficacy of penicillin therapy for syphilis, utilizing the proper dosage, treatment schedules, reactions, and complications were developed and evaluated by many dermatologic centers. Among the early cooperating dermatology clinics in this effort were the clinics of Stokes, Curtis, Cole, O'Leary, Callaway, Schoch, Leifer, Beerman, and Shaffer. Pillsbury and Sternberg, working in the armed forces with massive statistical material, also contributed immeasurably to our knowledge of syphilis therapy with penicillin. Olansky, Keirland and O'Leary, the Robinsons, and Rodriguez have studied antibiotics other than penicillin, which are effective in the management of syphilis, and Olansky and his associates have performed inoculation studies with the Treponema pallidum in human volunteers to give us a better understanding of the incubation period in the development of syphilitic infection. Rein, Sternberg, Pardo-Castello, and others have utilized penicillin successfully in the treatment of other treponemal diseases such as pinta, yaws, and bejel.

Dermatopathology—Histochemistry

In the field of dermatopathology and histochemistry, dermatologists have not only worked to promote an understanding of pathologic physiology, but by using special stains and other techniques, have done much to advance the field of pathology generally. Special stains developed by Neisser, Unna, Pappenheim, and others have enabled us to make a more careful differentiation between dermatologic and systemic conditions. Cawley and Wheeler, using Alcian blue periodic-acid-Schiff stain, have demonstrated that one can differentiate between scleroderma and dermatomyositis. Unna developed a spectroscopic analysis of fats, used digestive enzymes and demonstrated acid reactions of the nuclei, evaluated lipids during keratinization, and studied the chemical affinities of collagen. Blank and Laden's use of electronmicroscopy, Lever's electrolyte studies of blister fluids, capillary microscopy by Lorincz and Davis and the basic histochemical studies of Mescon and Shel-

ley, Urbach, Beerman, Brown-Falco, and Steigleder have added to the knowledge of dermatopathological problems.

In the more restricted field of dermatopathology generally one can but recognize the enormous contributions made by Gans, Unna, Pinkus, Sr., Pinkus, Jr., Weidman, N. P. Anderson, Lever, Caro, Beerman, Montgomery, Ketron, McCarthy, Sachs, Ellis, and other dermatopathologists.

Psychotherapy

Psychotherapy in skin conditions and the importance of the psyche in various dermatoses is admittedly controversial. The work of Stokes, Obermayer, Becker, Sr., Wright, MacKenna, Hodgson, Barber, Klauder, and others have demonstrated at least for certain conditions that psychic factors are important etiologically, and, in some instances, psychotherapy is as important as systemic and/or topical medication. Guy has used successfully "group psychotherapy" in the treatment of disseminated neurodermatitis. Heim, Bonjour, and Bloch demonstrated that psychotherapy of warts was as effective as any therapy available to them.

Leprosy

Here, too, dermatologists have contributed immeasurably to our knowledge of this systemic disease. The original work by Danielson, Boeck, and Hansen; the first staining of the bacillus causing leprosy done by Neisser and Hansen; Rabello, Jr.'s polar concept of leprosy; and the work of various dermatologists in evaluating the Mitsude skin test, have added to our knowledge of this disease. The Latin-American dermatologists, particularly at the International Congress on Leprosy in Havana, have helped to establish the modern classification of leprosy.

Cancer

Hutchinson recognized that malignant melanomas may arise from pigmented lesions of the nailbed, and, further, he recognized that cancer of the skin developed from arsenical keratoses. Bloch and Dreifuss, Yamagiva and Itchikawa were among the first to produce experimental tar cancers. The concept of the precancerous conditions was developed by Dubreillh and Bowen. Bloch recognized that carcinoma developed in x-ray burns. Hyde first recognized the influence of light in the production of skin cancer. Radcliff-Crocker was an early student of Paget's disease and recognized its carcinomatous import. The work of Graham-Little and Parks-Weber in superficial epitheliomas, and Queyrat's erythroplasia are also important additions to our concept of carcinoma generally. Dermatologists working with radium, x-ray therapy, Grenz therapy, and beta irradiation, have contributed much to the understanding of the management of carcinoma of the skin and lymphomatous diseases.

Serology

Wassermann, Neisser and Bruck first developed the complement-fixation test for syphilis, and, although the treponema immobilization test was not discovered by a dermatologist, Rein, Olansky, Miller and other dermatologists are responsible for much of the clinical evaluation of this phenomenon. Rein also was instrumental in evaluating the Reiter protein complement-fixation test for syphilis, as well as working with various serologic tests generally, and Olansky and his co-workers working with the immune-adherence test for syphilis and fluorescing treponema antibody tests have helped to develop other more specific serologic tests for syphilis.

Anatomy

Although working primarily in the field of cutaneous anatomy, Felix Pinkus, Hebra, Unna, and other European dermatologists developed the first basic understanding of anatomy of the skin. Simon's study on anatomy of the skin, Huxley's anatomy of the hair sheath, Unna's development of the concept of acanthosis, and his first description of plasma cells, all have been important in developing our concept of the

anatomy of the skin. More recently in this country studies by Winkelman on the sensory network of the skin, Lynch's study of elastic tissue in fetal skin, Tzanck's cytodiagnostic studies, the work of Van Scott on the anatomy of the sebaceous gland and hair, Kligman, Strauss, and Shelley's study on anatomy of the sebaceous gland, Shelley and Hurley's descriptions of the innervation of apocrine glands, Flesch and Esoda's studies on keratization cycles, Steiner's studies on connective tissue in the skin, Pinkus' adaptation of stripping of the skin by cellophane to study mitoses, the work of Shelley, Perry, and Hambrick on the anatomy of the ear, Zola Cooper's studies on mitotic rhythm in human epidermis, the work of Weidman on the yellowing dermatoses, the studies on pigmented nevi by Becker, Traub and Shaffer have added to our knowledge of basic anatomy, and studies by Sutton Jr. on embryology of epidermal neoplasia are noteworthy.

Occupational Dermatoses

Although occupational dermatoses affect primarily the skin, the organism generally may be involved by many industrial hazards. Anemias, asthma, carcinoma of the skin, cataracts, pulmonary fibrosis, jaundice, and even death may result from industrial or occupational dermatoses. Almost all substances from abietic acid to zapota gum may be responsible for industrial or occupational diseases, and Ramazzini was one of the first dermatologists to study industrial dermatoses. Since that time dermatologists have recognized the significance of systemic diseases, deep mycoses and related syndromes as being a part of certain occupational dermatoses. Protection of the public workers and consumers must be considered whether it be war gases, anthrax, sporotrichosis, or various dusts. Prosser-White, Schwartz, Tulipan, Peck, Warren, Birmingham, and Ronchese have made noteworthy contributions as they have recognized that the type of skin, race, sex, color, season, climate, diet, and age play a part. The time of onset, distribution, primary lesion, and systems involved are important, as well as the various chemicals, mechanical, biologic, bacteriologic, mycotic, and physical agents involved. Hellier, for example, has demonstrated that permanent clearing is greater after allergenic sensitization than after dermatitis caused by primary irritants.

Itching

Itching of the skin, whether it be due to dermatitis venenata, chigger bites, or systemic diseases such as lymphomas, jaundice, and the like, represents a challenge to medicine generally and not to dermatologists alone. The works of Rothman, Cormia's experimentally induced histamine pruritus, and more recently the work of Shelley and Arthur, who conceived the enzymatic basis for itching, in which the endopeptidases are responsible, have given us a new concept of the itching mechanism. Dermatologists have evaluated local and systemic medication in an effort to control this troublesome symptom.

Lupus Erythematosus

Lupus erythematosus of the discoid type was first recognized and described by Biett, Rayer, and Casenave. Kaposi first recognized the systemic manifestation of lupus erythematosus. J. Jadassohn observed the frequency of fever, mucous membrane involvement, and kidney involvement in systemic lupus erythematosus. After the LE cell was discovered, a dermatologist, Haserick, isolated the LE cell factor and showed this to be a γ-globulin as a fraction of the patient's serum which was responsible for the LE phenomenon. In the field of therapy, Russian dermatologists, Popoff and Kutinscheff, Prokoptchouk and Sorinson, Page in England, O'Leary and others in this country first used the antimalarial, Atabrine, in the treatment of discoid lupus erythematosus, and since that time various dermatologists have utilized other antimalarials such as Camoquin, Plaquenil, chloroquine, and other preparations alone and in combination in the treatment of discoid lupus erythematosus. O'Leary, Haserick, and

other dermatologists pioneered in the successful use of corticosteroid therapy for the control of systemic lupus erythematosus.

Endocrine

The work of Fitzpatrick and Lerner in the endocrine control of pigmentation, the work of Lorincz on the pituitary control of sebaceous glands, the work of Lamb and Lancaster on hormone therapy in polymorphic light sensitivity, the early work of Wile, Barney, and Bradbury on the urinary excretions of estrogens, and the use of estrogen therapy in acne by Andrews are noteworthy contributions. Callaway and his associates were able to demonstrate that extensive endocrinopathic investigation is not necessary in essential hirsutism in women if the patient has normal regular menstrual periods.

Drug Eruptions

Lorry was the first to recognize the systemic manifestations of drug eruptions. Hutchinson first recognized the significance of iodide eruptions and the occurrence of arsenical dermatoses. Wise and Abramowitz were among the first to give a clear description of the fixed-drug eruption. Dermatologists have shown that virtually every drug in our therapeutic armamentarium have at times been offenders, among the latest of which has been the recognition that penicillin in milk may be a cause of continuing chronic urticaria. Dermatologists are primarily responsible for recognition of the ecologic imbalance, photosensitizing character of certain drugs, and the interrelation between drugs as they affect the skin and hematopoietic system.

Vascular Diseases

Among dermatologic contributions in vascular conditions of the skin associated with systemic diseases are conditions such as Farber's description of hypertensive ischemic leg ulcers as a component of essential hypertension; Curtis pointing out the congenital absence of valves in the veins as the cause of varicosities; Montgomery's study of nodular vasculitis; L. Brunsting and associates bringing about a better understanding of the syndrome of pyoderma gangrenosum, while Keirland and his associates, Farber and Shelley, have further evaluated the syndrome of livedo reticularis. One may consider Schamberg's progressive pigmentary dermatosis, Majocchi's purpura annularis telangiectodes, and the pigment purpuric lichenoid dermatosis of Gougerot-Blum in the same category, but all represent basically a vascular disease. Kaposi's idiopathic hemorrhagic sarcoma must also be considered as a systemic vascular disease complex.

Physiology

The past generation has seen the morphologic age of dermatology develop into the physiologic. It is almost impossible to evaluate and to assign proper credit to the people who have worked in the field of physiology of the skin, which indirectly affects basic physiology. The role of the skin in thermal regulation as elaborated by Herrmann, Sulzberger, and Rothman; the problem of sweat retention as evaluated by Shelley, Weidman, Horvath, Pillsbury, Sulzberger, and Herrmann; studies of pH of the skin by I. H. Blank; the concept of the acid mantle as developed by Marchionini and further studied by Cornbleet and Pillsbury; percutaneous absorption studies by Rothman and his associates; the predominance of vagatonia in the atopic, a concept demonstrated by Brill; the physiology of the development of urticaria; the demonstration by Riley and West that the source of histamine release is in mast cells and not in epidermal cells; apocrine sweat gland physiology as elaborated by Shelley and Hurley; a study of the histamine levels in human skin by H. H. Johnson Jr.; the studies by Stoughton and Lorincz on the action of collagenase and anticollagenase factors in human serum; Lever's studies on the electrolyte content of blister fluid; Shelley, Perry, and Hambrick's study of the physiology of the external ear and its oil and sweat glands; the physiology of the

apocrine glands by Shelley and Perry; the physiology of the eccrine glands by Lobitz and Dobson; the physiology of sweating in which Lobitz, Hermann, Rothmann, Sulzberger, Shelley, Pillsbury, and others played such an important role; sensory functions of the skin, such as itching, with Rothman, Shelley, Arthur, Melton, Cormia, Konigstein, etc. Literally there is no stopping place in such a review.

Lipid Diseases

Contributions by dermatologists to the lipid diseases are numerous, among which are the works by Grutz, who first recognized idiopathic hyperlipemia; studies by Lever on idiopathic hyperlipemia and particularly inhibition of lipemia by clearing factors; primary hypercholesteremia xanthomatosis as studied by Curtis and his associates; lipid studies in xanthomas by Urbach, Oppenheim, Wile, and Epstein; the recognition of necrobiosis lipoidica diabeticorum by Urbach and Oppenheim; and particularly Urbach's contribution to the histochemical and metabolic studies in the constitutional disease lipoid proteniosis. Wheatley, Nicolaides and associates have carried out extensive laboratory fat studies.

Collagen Diseases

Under the category of collagen diseases, the study by O'Leary and his colleagues on muscle in cutaneous and systemic disease, in which they did combined skin and muscle biopsies and electromyography is outstanding. The work on systemic amyloidosis by Rukavina, Curtis, and Bloch, Nomland's test for amyloid, O'Leary and Waisman's studies on dermatomyositis, and the combined efforts of many dermatologists on scleroderma, scleredema, periarteritis, and nodular vasculitis have kept dermatology in the forefront in this broad field.

Sarcoidosis

In sarcoidosis dermatologists have been particularly outstanding in an attempt to evaluate this problem. The work of Besnier, Boeck, Goeckerman, Michelson, Kveim, and Nelson cannot be overstated. The deep sarcoids as described by Darier and Roussy, angiolupoid of Brocq and Pautrier, Besnier's lupus pernio and Wende's nodular tuberculosis of the hypoderm, probably represent various phases in the syndrome of sarcoidosis.

Miscellaneous

There are many contributions that do not necessarily fit into a specific category yet are very important as far as dermatology's contribution to the progress of medicine.

Who can measure the contributions of Michelson in our understanding of tuberculosis of the skin and sarcoidosis? L. Brunsting is responsible in the main for our understanding of the various porphyria diseases. Huriez's study of cutaneous tuberculosis enabled us to understand this problem more clearly. Other noteworthy dermatologic contributions have been Lamb's clinical and endocrinologic studies of polymorphic light sensitivity; Carlborg's work on decreased arterial pulsations in pseudoxanthoma elasticum; Wile's observation on the variations and mutations in the various lymphomas, and the work of Price, who developed the concept that angiokeratoma corporis diffusum has associated abnormalities in other organs and in other systems. Buscke's elaboration of the syndrome of scleredema adultorum; Gilchrist's first recognition of x-ray damage to the skin; and Behcet's description of the triple symptom complex as a systemic disease; Ingram and Pillsbury's description and explanation of the syndrome of circumscribed myxedema; Bluefarb's description of the cutaneous manifestations of polycythemia vera; the Ehler's Danlos syndrome; and Hailey-Hailey description of familial benign chronic pemphigus. Notable are: Hitch's adaptation of the Papanicolaou cancer smear to biopsies of the skin; Sagher, who first described the systemic nature of urticaria pigmentosa and who found Tzanck cells on the cervix; Pardo-Castello and Heller's treatise on nail diseases; Bazin's

recognition and description of erythema induratum; Ailbert's description of the systemic disease, mycosis fungoides; Hebra's description of erythema multiforme; Willan's description of erythema nodosum; Kierland's description of the cutaneous manifestations of the functioning carcinoid; and Addison's description of the xanthomas. The description of pseudoxanthoma elasticum by Gronblad Strandberg; Livingood's large series of cutaneous diphtheria, the recognition and description of incontentia pigmenti by Jadassohn and Sulzberger; the description of prophyria cutanea tarda by L. Brunsting; Duhring's description of dermatitis herpetiformis; Degos' description of the fatal cutaneointestinal syndrome of papulosis atrophicans maligna; Ayres' and Ayres' recognition of variations in pyoderma gangrenosum; and the relationship between carcinoma and scleroderma, carcinoma and dermatomyositis as studied by Christianson, Brunsting, and Perry. Dermatologists have contributed to our knowledge of genetics as they affect various skin and systemic diseases, such as Darier's disease, pseudoxanthoma elasticum, gynecomastia, xanthomatosis and amyloidosis.

Treatment

Purely dermatologic therapy will not be discussed unless it has implications that involve medicine generally. However, from Whitfield's use of salicylic acid and benzoic acid in the treatment of ordinary superficial fungus infections of the feet to the utilization by Blank and subsequent study by Rhiel, Pardo-Castello, and others that griseofulvin may be given by mouth to treat certain superficial fungus infections of the skin, nails, and hair, dermatologists have made many significant contributions. Hudelo and Robut first used bismuth in the treatment of lupus erythematosus. Bal has been used in the treatment of many heavy metal dermatoses and heavy metal intoxication. Mayer developed Pyribenzamine; Curtis and Owens first used Benadryl in urticaria; Schamberg, during World War I, was responsible for the synthesis in this country of arsphenamine and neo-arsphenamine. Ruete used gold therapy in lupus erythematosus before it was ever used in arthritis. Pusey developed carbon dioxide snow in the treatment of various dermatoses. S. A. M. Johnson and his associates have used chelation in porphyria and other systemic diseases. Rostenberg used malonate as an inhibitor of sweating by blocking an enzyme system. Curtis and his associates developed the stilbamidine treatment for deep fungus infections and more recently Harrell has used amphotericin B intravenously in blastomycosis successfully, and other uses of amphotericin B by Sternberg, Newcomer, and Costello in various deep mycoses has been noteworthy. The successful use and dangers of sulfonamide drug therapy, the various systemic antibiotic medications, from the introduction of penicillin to the very latest of the antibiotics has been greatly influenced by dermatologic observation and uses. The local uses of antibiotics in various combinations has developed as a result of contributions by virtually every dermatologist in the country. More recently, the use of steroids systemically and locally in various combinations, with and without antibiotics, with an evaluation of their indications, contraindications and dangers, have been the result of many contributing dermatologists. Kurtin, Blau, Orentriech, Burks, Wilson, Rattner, Epstein, and others have pioneered in the use of dermabrasion therapy for scars, senile skin, pigmentation problems, etc. Dermatologists are also participating in the evaluation of ultrasonic waves in varying dermatologic disorders.

I approach the end of this discussion more confused and more frustrated than when I started. Although I have tried to present a résumé of dermatology's great contribution to the progress of medicine, I am sure that I have unintentionally overlooked many significant contributions.

In an abbreviated summary, may I list a few of the accomplishments dermatolo-

gists have made to the progress of medicine generally:

1. Discovery of the causative organism of syphilis
2. Development of the complement-fixation serologic test for syphilis
3. Evaluation of the treponema immobilization test for syphilis
4. Development and evaluation of spirochetal antigens for the diagnosis of syphilis
5. Human inoculation studies in syphilis
6. Clinical cooperative group studies in syphilis
7. Long-term evaluation of untreated syphilis
8. Utilization of penicillin in the treatment of syphilis
9. Utilization of antibiotics other than penicillin in the treatment of syphilis
10. Discovery of the organism causing gonorrhea
11. Demonstration of the organism causing chancroid
12. Isolation and discovery of the organism causing rhinoscleroma
13. Discovery of the organism causing cryptococcosis (European blastomycosis)
14. Staining and identification of the lepra bacillus
15. Discovery of the organism causing pinta
16. Successful treatment of the treponemal diseases (pinta, bejel, and yaws) with penicillin
17. Demonstration of the transmissibility of virus diseases and the recognition of inclusion bodies and multinucleated giant cells in virus diseases
18. Demonstration of the causative organism of coccidioidomycosis
19. Demonstration of the causative organism of North American blastomycosis
20. Demonstration of the causative organism of South American blastomycosis
21. Recognition and description of lymphogranuloma venereum as a separate veneral disease.
22. Development of a specific intradermal skin test for lymphogranuloma venereum
23. Development of the complement-fixation test for lymphogranuloma venereum
24. Development of a specific skin test for South American leishmaniasis
25. Development of a specific skin test for sarcoidosis and an understanding of sarcoidosis as a systemic disease process
26. Discovery of the protein, cryoglobulin, and description of the syndrome of cryoglobulinemia
27. Isolation of the MSH factor
28. Isolation of the antiMSH factor
29. Elucidation of the pigment metabolism mechanism
30. Recognition of the photodynamic action of light and application of ultraviolet light therapy to disease
31. Recognition of light as a cause of carcinoma of the skin
32. The development of passive transfer studies for immunologic procedures
33. Recognition of autosensitization and its relation to the autoimmune mechanism
34. A development of the concept that a focus of infection releasing micro-organisms or part or ingredients of these micro-organisms produce the id reaction
35. First demonstration of tar carcinogenesis
36. Development of the concept of precancerosis
37. Evaluation of occupational and industrial hazards in cutaneous and in systemic disease
38. The development of special stains and procedures for dermatopathology and histochemistry
39. An understanding of genetics as they affect skin conditions
40. A complete reevaluation of physiology of the skin as it affects itching, sweating, sebaceous gland activity, pigmentation, sensitization, etc.
41. Contributions to our knowledge of vascular physiology
42. Contributions to our knowledge of endocrine physiology
43. Important role in the diagnosis and management of "collagen diseases"

44. Contributions to our understanding of lymphomatous diseases, particularly in immuniology and therapy
45. Contributions to the study and evaluation of virus diseases, specifically orf, lymphogranuloma venereum, Milker's nodules, herpes simplex, warts, herpes zoster, etc.
46. Contributions to vitamin deficiency diseases and rational vitamin therapy
47. Contributions to tissue culture techniques
48. Introduction of dermabrasion therapy
49. Contributions to the specific systemic treatment of the deep mycoses and understanding of the immunology of the deep mycoses
50. Important roles in the development of antihistamines and subsequent use of antihistamine therapy
51. An important role in the evaluations of antibiotics, parenterally and locally, for systemic and cutaneous disease
52. Important roles in the evaluations of corticosteroid therapy, systemically and locally
53. The use of chelation in systemic diseases
54. Important role in evaluating stilbamidine, amphotericin B and other medications for deep mycoses
55. Development of and utilization of griseofulvin in the treatment of certain superficial fungus infections
56. Important role in medical education
57. Important roles in the development of proper dosage, complications, and study of the long-range effects of all forms of radiant energy
58. Contributions to biochemical and histochemical techniques
59. Contributions to histopathologic techniques (special stains, electronmicroscopy, etc.)
60. Important role in applications of psychotherapy to certain cutaneous disorders
61. Description of specific cutaneous disease syndromes and contributions to the study and understanding of the skin and medically interrelated diseases
62. Important role in the study of aging

From this report, I think that all dermatologists can take pride in their specialty and recognize that dermatologists and dermatology may well hold their heads high and point with pride to their contributions and accomplishments.

Duke Hospital.

The Aged Human Sebaceous Gland

The Effects of Hormone Administration and a Comparison with Adolescent Gland Function

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Introduction

A new technique for measuring the sebum excretion rate has been developed. It eliminates some of the errors inherent in other methods.

The amount of sebum excreted by the sebaceous gland has been shown to be influenced by several major factors. Miescher and Schönberg[20] have demonstrated that the amount of sebum excreted is dependent upon the size of the sebaceous gland. The larger the gland, the more sebum excreted, and vice versa. The size of the gland changes with age. Prior to puberty, in the human the sebaceous gland is small, and little sebum is excreted.[7,23] At puberty there is a great increase in sebum excretion which continues through adolescence.[14,16] There are conflicting reports as to whether adolescent males[7,16,28] or females[5] have a higher level of sebum excretion, but aged women have a much lower level of sebum excretion than aged men.[3,12,13,28] With increasing age, men have little or no change in sebaceous gland excretion.[12,16]

Sex hormones influence sebaceous gland excretion. In castrate or eunuchoid males, administration of testosterone produces sebaceous hyperplasia.[9] In normal prepubertal males, testosterone also produces sebaceous gland hyperplasia.[21] The recent work of Rothman, Lorincz and co-workers[10,17,18] indicates that progesterone in combination with a hormone from the anterior pituitary gland, sebotropin,[19] causes sebaceous gland hyperplasia in animals. This finding offers for the first time convincing explanations for sebaceous hyperplasia in females at puberty coinciding with the onset of ovarian production of progesterone and for the decrease in sebum excretion in aged women occurring at the end of ovarian functional activity. Also, it has been possible to produce or aggravate acneform lesions in young women with progesterone.[1,29] Whether the recent demonstration of the synthesis of testosterone from progesterone by human ovarian[24] and testicular tissue[25,26] indicates that progesterone may act as an androgen in sebaceous hyperplasia is not as yet known.

It was the purpose of this study to evaluate the effects of parenterally administered testosterone and progesterone on the aged sebaceous gland of males and females, respectively, and to compare them with normal untreated adolescent control persons of both sexes. To do this a simple quantitative method of measuring the sebaceous excretion rate without affecting sebum production or delivery has been developed.

Materials and Methods

There are a variety of techniques for measuring sebaceous gland excretion.[2,4,11,15,22] The techniques used in these studies utilized the reduction of osmic acid by sebum absorbed on filter paper.[2,4,6,8] The subjects' foreheads were defatted five times with ether-soaked cotton pledgets. Whatman filter paper No. 42 was placed on the forehead under square pieces of sponge rubber with pressure

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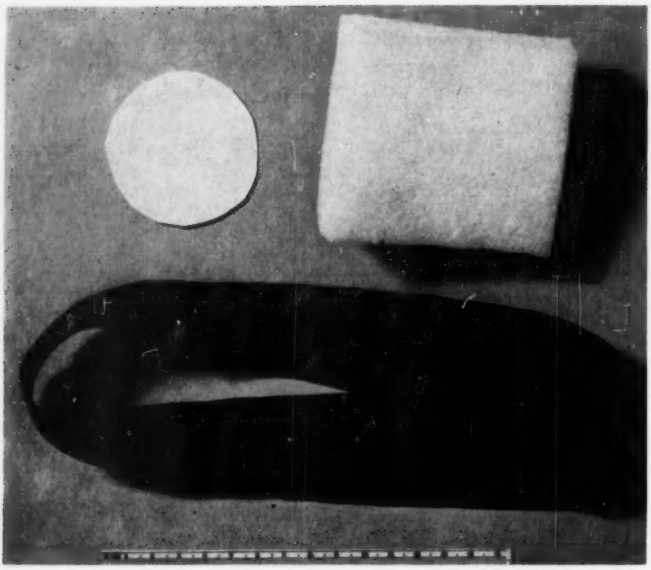
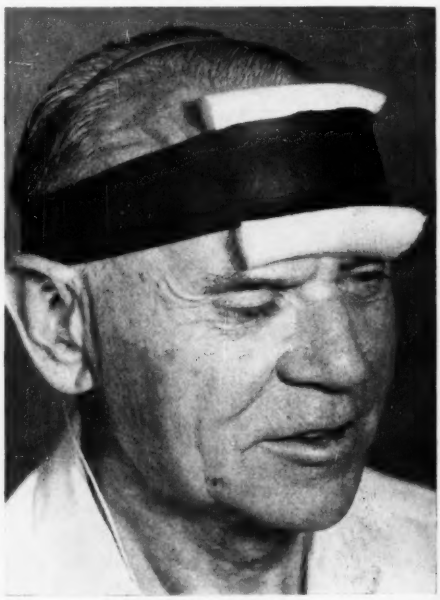


Fig. 1.—Whatman filter paper No. 42 with sponge rubber and band of rubber for holding sponge and paper in place on the forehead.

from a band of rubber (Figs. 1, 2). Fresh papers were applied continuously in the same location at 5-minute intervals for periods of 30-40 minutes. After removal of the papers from the forehead, they were exposed to the fumes of 5 ml. of 2% osmic acid over a tissue dialysis chamber with the surface previously in contact with the skin facing down (Fig. 3). The zone consisting of the peripheral 8 mm. of the paper was not developed or read on the densitometer, for it served as an absorptive band preventing flow of sebum emulsified by sweat from flowing into the area. Each paper was developed for a period of two minutes. The papers are blackened because of reduction of the osmic acid by unsaturated bonds in the sebum absorbed on the filter paper.[27] Darkening of these papers continues for a period of 24 hours after exposure to osmic acid fumes[2]; therefore all papers were read at least 72 hours after development. The papers were cut to fit into the 35 mm. negative plate holder of a photographic enlarger (Fig. 4). The plate holder was then inserted into the enlarger (Fig. 5) and light transmission through the paper was read on a Photovolt photoelectric exposure photometer (Model 200-M) in a fixed standard position. Prior to the reading of any papers, the densitometer was calibrated to read zero with no light reaching the photoelectric cells and 100 with an untreated No. 42 Whatman filter paper in the negative plate holder. Fresh filter paper exposed to osmic acid fumes did not darken and gave the same densitometric reading as fresh unexposed paper. The current supply to the enlarger was a 6-volt storage battery utilizing a 6-volt bulb. This was used to eliminate the effect of line voltage variation on the light source. All readings were subtracted from 100 so that larger numbers would indicate greater amounts of sebum.

Fig. 2.—Filter paper in place under the sponge on the forehead of an aged subject.



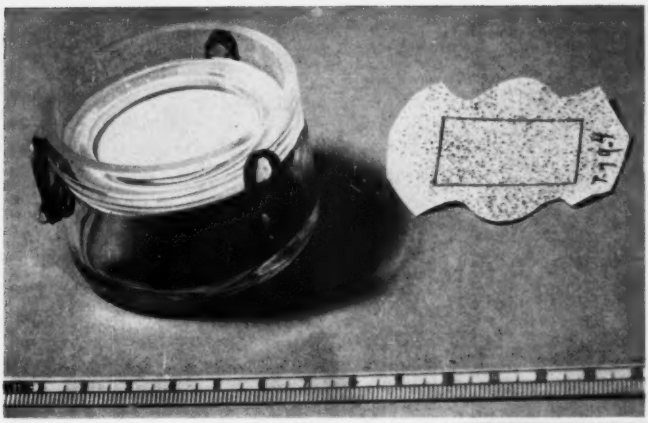


Fig. 3.—Chamber used for developing filter papers over 2% osmic acid. On the right a developed paper. The area through which light passes for densitometric reading is enclosed in a rectangle.

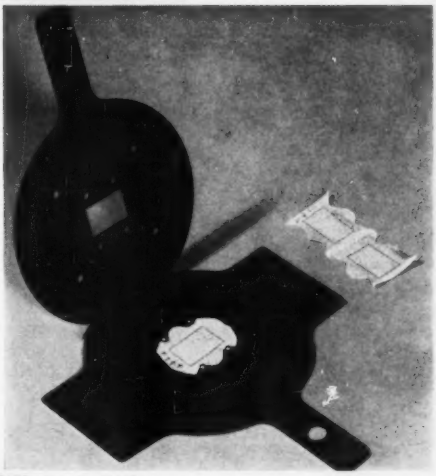


Fig. 4.—Developed paper in place in 35 mm. negative holder.

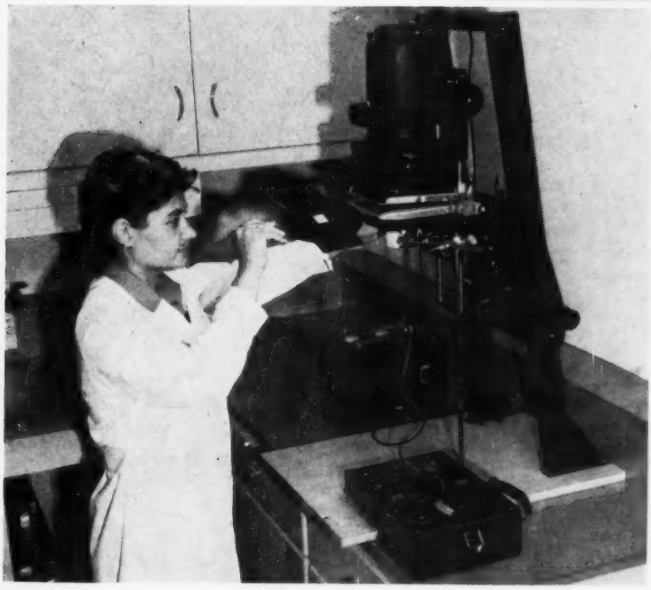


Fig. 5.—Negative holder being placed in photographic enlarger for densitometric reading. The densitometer is in the lower right hand corner.

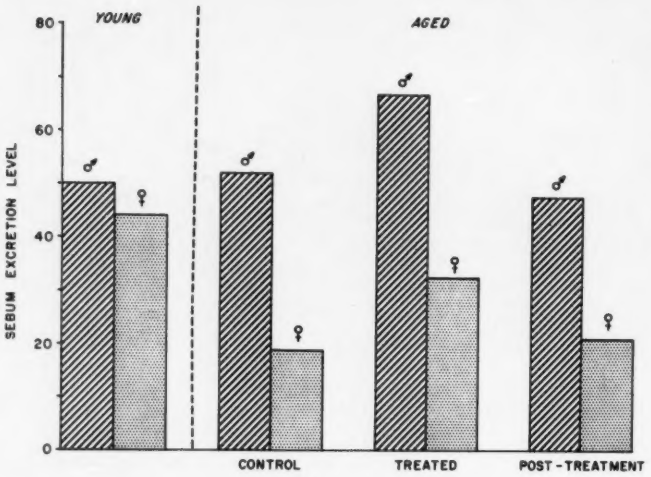


Fig. 6.—Mean values of the sebum excretion rates for young males and females and aged males and females, before, during, and seven weeks after treatment with hormones.

The values measured by this technique will be referred to as the sebaceous gland excretion rate,[22] since the sebum is being removed by the absorbent filter paper as rapidly as it is delivered to the surface. Whether sebum delivery is by flow or via a "wick"[18] of keratin lining the pilosebaceous orifices, it was found using this technique that values remained fairly constant in a given person even when fresh papers were applied every five minutes for as long as four hours.

The sebaceous gland excretion level of five females, aged 15 to 17 years, and six males, aged 15 to 18 years, was determined with this technique. Similar studies were carried out on five females, aged 70 to 87 years, and four males, aged 73 to 82 years. After control studies had been obtained on four consecutive days on the aged men and women, 1 ml. of testosterone enanthate in sesame oil * was administered intramuscularly to the males, and 2 ml. of hydroxyprogesterone caproate in sesame oil † were administered intramuscularly to the females at weekly intervals for a period of five weeks. After these five injections, sebum tests were again performed on the aged group for four consecutive days. Seven weeks after receiving their last injections, sebum tests were repeated on the group of aged males and females for three consecutive days.

The excretion tests were performed on the aged subjects during the months of May, June, and August, and on the adolescents in June in a constant temperature, constant humidity, air-conditioned environment in which sweating of the subjects was minimal. All results were evaluated statistically using the *t* test.

* Supplied as Delatestryl by E. R. Squibb & Sons (each ml. contains 200 mgm. testosterone enanthate)

† Supplied as Delalutin by E. R. Squibb & Sons (each ml. contains 125 mg. hydroxyprogesterone caproate).

Results

Table 1 gives the ages of the elderly subjects with the mean values of sebaceous excretion before (control), during (treatment), and seven weeks after cessation of hormone treatment (post-treatment), individually and by sex.

Each excretion rate is the mean of at least six determinations a day for three or four consecutive days and represents 21-32 individual determinations.

TABLE 1.—*Sebum Excretion Rates in the Aged*

Female	Age	Control Rate	Treatment Rate	Post-Treatment Rate
G	70	26.6	38.6	26.6
S	71	21.6	36.7	22.7
K	78	7.8	19.3	7.1
B	80	17.6	33.4	29.9
H	87	21.5	34.4	20.3
Male				
Ga	73	49.9	69.8	45.0
Go	73	59.4	70.3	39.3
Ma	82	61.2	76.1	58.7
Me	79	38.2	52.6	not done

The individual mean differences between control and treatment, treatment and post-treatment, and control and post-treatment were evaluated using the *t* test of statistical significance. The individual differences between the control and treatment, and treatment and post-treatment were highly significant statistically ($P<0.01$) for the females. For the aged males the difference between the control and treatment was highly significant ($P<0.01$), and it also was significant between treatment and post-treatment ($P<0.05$). There was no statistical difference, however, between the control and post-treatment values for both the males and the females ($P>0.05$). Therefore, the change in sebaceous excretion occurring after the hormone therapy was significant, as was the drop seven weeks after it was stopped. The control values and the post-treatment values were not significantly different, indicating the sebum excretion rate had returned to pretreatment values.

The difference between the control values for the aged males and females was also highly significant statistically ($P<0.001$), indicating a real lowering of sebaceous excretion of the aged female as compared with the aged male. There was also still a difference, on statistical analysis, between the treatment value for the aged females and the control value for the aged males ($0.05>P>0.01$). Progesterone therapy thus had raised the level of sebum excretion in the aged female but still not to the level of the aged male.

Table 2 gives the mean values for the adolescent persons calculated from the results of four consecutive days of testing forty minutes daily. Using the *t* test there was no significant difference between the values for the adolescent males and females ($P>0.05$), or the adolescent and aged males ($P>0.05$). There was no significant difference ($P>0.05$) between the adolescent males and the aged males after testosterone treatment, indicating that the sebaceous excretion of the treated aged males had not become significantly greater than that for the normal adolescents. The difference between the adolescent and aged females was highly significant ($P<0.01$). However, following progesterone treatment, there was no significant difference ($P>0.05$) between the treated aged and adolescent females, indicating that progesterone had raised the sebum excretion of the aged females to an adolescent level!

TABLE 2.—*Sebum Excretion Rates in the Young*

Female	Age	Excretion Rate
K	15	49.4
P	15	31.3
R	15	37.7
S	16	52.5
R	17	48.8
Male		
D	15	62.4
Du	15	44.2
G	15	37.9
S	15	43.0
K	17	51.8
W	18	60.1

Figure 6 compares mean sebaceous excretion rates for the young males and females; and the aged males and females before, during, and seven weeks after hormone treatment.

Comment

The absence of any significant change in the level of sebaceous excretion in the male with age was confirmed. Ma (Table 1), who had the highest sebaceous excretion level of the aged males, also suffered from Parkinson's disease. This, as well as the findings of Miescher and Schönberg,[20] suggests that the increase in sebaceous gland excretion occurring in some aged males as reported by Kirk [12] was probably due to the presence of Parkinson's disease in some of his subjects. Just as the prepuberal sebaceous gland responds to testosterone,[21] so does the aged gland. Were it not for the influence of other factors, such as Parkinson's disease, on sebaceous excretion, such a test as has been used in this study might be useful in determining androgen production by biological assay in the male.

The puzzling lowering of sebum excretion in the aged female probably is explained by the findings of Rothman and Lorincz on the effects of progestrone and sebotropin in animals.[10,17-19] The finding that progesterone administration to the aged female raises her sebum excretion to adolescent levels not only serves to confirm this work in humans but also may be indicative that sebotropin liberation by the anterior pituitary gland in the human continues unabated with age, and that the decrease in sebaceous gland size and function in the aged females relates solely to the reduction of progesterone production of the ovaries at the menopause due to the cessation of the monthly formation of the corpus luteum.

The return to pretreatment excretion levels in both males and females seven weeks after discontinuation of therapy seems to emphasize the exquisite and constant influence testosterone and progesterone have on the male and female sebaceous glands respectively.

Summary

Using a refined technique of measuring sebaceous gland excretion by measuring densitometrically the amount of osmic acid reduced on filter papers applied to the forehead for 30-40 minutes daily over a 3-4-day period:

The absence of a significant difference in sebaceous gland excretion of the adolescent male and female was confirmed.

The finding of no significant difference in sebaceous gland excretion of the aged male as compared with the adolescent male was confirmed.

The decrease of sebaceous gland function in the aged female as compared with the adolescent female was also confirmed.

The aged male sebaceous gland responded to the administration of parenteral testosterone with increased excretion.

The aged female sebaceous gland responded to the administration of parenteral progesterone with an increase in excretion to levels not significantly different from that of the adolescent female gland.

These increases in glandular function were temporary and excretion levels returned to pretreatment range within seven weeks of cessation of hormone administration.

Grateful acknowledgement is made to Miss Iris Kiem, who performed the statistical evaluation of these studies, to Dr. Harvey Blank, who made many valuable suggestions, and to Felix R. Brunot for technical assistance.

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ABSTRACT OF DISCUSSION

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: Let us first congratulate Dr. Smith on winning the Association's Essay Medal in the face of highly creditable competition and on his fine work and clear presentation. The enthusiasm, diligence, and promise of young men, on whose capable shoulders falls responsibility for the future of our scientific field, are stimulating and refreshing.

I think it interesting to call to memory the contributions of previous medalists, of whom Dr. Smith is the ninth. The new becomes old as the years pass swiftly. The first winning essay, in 1951, was Thomas Fitzpatrick's, "The Tyrosinase Reaction as an Index of Malignancy of Pigment-Cell Neoplasms." The second was by Paul Rosahn, "The Adverse Influences of Syphilitic Infection on the Longevity of Mice and Men." The third was by Joseph Brennan, "Contributions to the Study of Pemphigus," wherein he compared experimentally produced blisters with those of pemphigus in 1953 when the significance of acantholysis was novel. The fourth was by Albert Kilgman, "The Pathogenesis of Tinea Capitis Due to Microsporum audouini and Microsporum canis." The fifth was by David Kersting and Elson Helwig, "Eccrine Spiradenoma, the Painful Adenoma of Eccrine Sweat Gland." The sixth was by Alfred Kopf, "Histochemical Studies of the Distribution of Alkaline Phosphatase in Normal and Pathologic Human Skin." The seventh was by Peter Flesch and Elizabeth Esoda, "Defective Epidermal Protein Metabolism in Psoriasis." And the eighth, last year, was that of Thomas Fitzpatrick, newly elected to membership in our Association, whereby he won another Oscar—I mean medal—with his essay on "The Nature of Hair Pigment."

While the interests of these investigators have been widely distributed, one notes the modern trend toward viewing pathology from the standpoint of chemistry, a field in which many of us are rather disconcertingly behind the times. When I discussed elementary chemistry with a student presently doing freshman premedical work at Massachusetts Institute of Technology, I was tagged out the instant I mentioned "valence," for youth is learning chemistry in terms of atomic physics and the interactions of electron shells, and "valence" is a dodo.

That is a line Walter Wilson would never pass by. With apologies to Walt, and to other poets who treat the English language with even greater consideration. I propose to burst into song. My title, "Valence is a Dodo."

Valence is deceased, defunct,
By-gone, and of the past.
Like many things that Science brings,
It came, but did not last;
It flourished, then it perished
Like the ammonites of yore,
A horse and buggy of the age
Ere satellites would soar.

O! Valence is the twilight,
Electrons are the dawn!
We believed in it in toto—
In toto we were wrong;
For Valence is a dodo,
And Science marches on.

Gentlemen, it is not every year that our Association receives a message so inspirational, touching, wistful, so pregnant with *Weltschmertz*—and for this, we may thank God!

We of the older generation, then, are obliged to find ways of yielding graciously to the next, even if they are not likely to turn out to be much wiser than ourselves. What we are able to teach them is what is learned best by living a long time: resourcefulness in using simple means, and the attributes of medical maturity, patience, understanding, and concern for people, that bespeak, not the disciplined and impersonal investigator of defects, but the friend of human beings who need help, the things that sometimes do a patient about as much good as pills, salves, and "shots."

Dr. Smith has confirmed and established certain facts about sebaceous gland function, in particular, the equality, for practical purposes, of sebaceous secretory activity in aged and adolescent males; the inequality in aged and adolescent females; the responsiveness of the glands in aged males to injections of testosterone; the responsiveness in aged females to injections of progesterone; and the transitory effects of these chemicals.

I should note that Dr. Smith's method of estimating secretion compares quantities but does not yield quantitative measurements, nor does he claim for the numbers obtained with his ingenious densitometric technique a linear relationship to actual quantities: his reading of "60" does not imply twice as much sebum as a reading of "30." An endeavor to weigh the secretion, however, would entail variables difficult of extrication due, for example, to sweat, humidity, and epidermal débris. The results of his comparatively abstract study relate science to the clinical fact that progesterone and testosterone can make acne appear, or, if it is already present, can make it worse.

In closing, I wish to employ again words our respected friend, Stephen Rothman, used in his comment on the medalist's paper of 1956: "We are all proud of your work," Dr. Smith, "and trust that you will continue to contribute to the advancement of dermatology."

DR. STEPHEN ROTHMAN, Chicago: I have been delighted listening to the fine presentation of Dr. Smith's beautiful work.

After it was shown in our laboratory that progesterone caused sebaceous gland hyperplasia, the validity of this finding had been doubted. It was even claimed that progesterone is an effective therapeutic agent in the treatment of acne vulgaris. Most recently, A. Jarrett has published experimental data from the University College Hospital in London (*Brit. J. Dermat.* 71:102, 1959) indicating that progesterone is without effect on the sebaceous glands in intact animals. He assumed that the effects we observed could be obtained only in spayed animals. In contrast, however, Zeligman and Hubener at John Hopkins (A.M.A. ARCH. DERMAT. 76:652, 1957) succeeded in producing seborrhea and acne in adult healthy females by administation of large doses of progesterone. I am indeed happy with the clearcut results of Dr. Smith demonstrating beyond doubt that progesterone restores to full activity the senescent sebaceous glands of elderly women.

The differences in his pre- and post-treatment values are so good that they are obviously highly significant. I should, however, like to ask two questions. Are the figures presented a measure of darkening in a linear fashion? And did the author perform any experiments to find out whether the absolute amount of sebum is proportionate to the amount of unsaturated fatty acids which he has measured?

DR. SAMUEL M. PECK, New York: The dermatologist is often accused of using glandular therapy empirically, without any basis in fact. As a matter of fact, we have to walk very carefully when we are part of a department in a large institution in prescribing endocrine therapy, especially when we are called in consultation.

For many years, as I am sure many of you have, at least I have, been very happy to have a modality at my disposal in treating pruritus hiemalis, which is a frequent clinical entity in New York City. My routine treatment was injection of 25 mg. of testosterone once a week. I always explained to the patient that the reason I was able to control the itching so that they needed less and less therapy to the effective parts, which usually are the lower legs, was the fact that I stimulated sebaceous gland activity. I used it empirically, 25 mg. a week. I do not know the dosage the essayist used, but one of my observations was that, after giving injections once a

week for four or five weeks, the results continued for a month or longer. Now, I see, he has had a period of seven weeks in which an actual increase in sebaceous gland secretion could be demonstrated.

DR. FRANK E. CORMIA, New York: I have a short comment and perhaps a suggestion for Dr. Smith. We are all familiar with the clinical beneficial effects of estrogenic hormone in acne and have used it either continuously or cyclically, most likely the latter. While we do not exactly know how it works, it probably affects the size of the sebaceous glands.

There is considerable loose thinking in the current literature about the effects of estrogens, and it might be worth while for Dr. Smith to use estrogens to evaluate their effect upon the aging sebaceous glands, in both males and females.

DR. J. GRAHAM SMITH JR., Miami, Fla. (Closing):

I should like to thank all the discussors for their kindness. The point raised by Drs. Sutton, Rothman, and Mescon concerning the relation of the amount of sebum as measured by the densitometric reading of osmic acid-darkened material and the actual weight of sebum excreted is not settled. The osmic acid darkening is due to the presence of unsaturated bonds in the lipids absorbed on the filter paper and presumably, as the relative number of unsaturated bonds increases, so does the amount of sebum. In our laboratory, the actual weight of sebum excreted is being correlated with densitometric readings in the same patient. Dr. John Strauss of Dr. Mescon's department is also investigating this problem.

The figures for sebaceous excretion in the tables are, as Dr. Sutton mentioned, relative figures and are not actual amounts. It is possible to quantitate the densitometric technique to some extent using graded dilutions of cod liver oil in acetone, but it is obvious that cod liver oil and sebum are very different materials. We also are studying squalene and olive oil as unsaturated materials.

In answer to Dr. Peck, it may be of interest that it was possible in one patient, in her late seventies, to produce an acneform eruption. This was the first pustular lesion this patient had had in over sixty years.

Also, I did not mean to imply that these injections were being given for therapeutic benefit. They were not. This was done purely as a research procedure, and it was done after a very complete and thorough consultation with our endocrinologist, who gave his approval to the study.

Neutron Activation Analysis of Arsenic in Normal Skin, Keratoses, and Epitheliomas

ANTHONY N. DOMONKOS, M.D., New York

In 1888, Hutchinson [1] ascribed arsenic as the cause of epitheliomas and keratoses occurring in patients with a history of ingestion of potassium arsenite solution (Fowler's solution) for medicinal purposes. Since then, sufficient quantitative data has not been available to evaluate the etiologic significance of the actual amount of arsenic contained, not only in the arsenical epitheliomas, but also in keratoses and normal skin.

This study was undertaken to determine the amount of arsenic found in normal skin, epitheliomas, and keratoses in patients with a history of arsenic ingestion and to compare these amounts with those found in normal skin, epitheliomas, and keratoses occurring in patients with no arsenic history. With the results of these findings it was anticipated that there would be further elucidation as to whether there is an increased amount of arsenic in arsenical epitheliomas in comparison to that of the adjacent normal skin and to epitheliomas in patients with no arsenic history.

In 1923, Billeter and Marfurt [2] reported on the arsenic content of various organs. On the basis of some 9 specimens of skin, they reported the average value of skin to be 0.097μg. per gm. of tissue.

In 1925, Osborne [3] performed microchemical studies of arsenic in arsenical pigmentation and keratoses. In 1928, Osborne [4] elaborated on his findings in regard to arsenic in the skin. He found no relationship between amounts of arsenic in the skin and the development of epitheliomas.

In 1935, Montgomery [5] and in 1941, Montgomery and Waisman [6] were able to show in a few cases of superficial epithelioma less arsenic than in the normal adjacent skin. In arsenical epithelioma, the quantity of arsenic was more than in the adjacent normal skin. Osborne's microchemical method and the Osterburg modification of the Gutzeit method were used.

Recently, nuclear science has created a new analytical procedure for the determination of trace quantities of many elements. This procedure, called neutron activation analysis, utilizes nuclear particles formed in the chain-reacting pile to react with a stable element such as arsenic, to produce a radioactive isotope of arsenic. Quantitation is then accomplished by determining the amount of radioactive arsenic with the Geiger-Müller counter.

In 1958, Scott [7] utilized this form of analysis for arsenic. He found an increased amount of arsenic in the normal skin and in the lesions of keratoses and epitheliomas developing in those patients with a history of external contact with arsenic or ingestion of arsenic.

Material

One or more specimens comprising the epidermis and the upper dermis were submitted to neutron activation analysis for arsenic from 27 patients with a history of Fowler's solution ingestion and from 57 patients with no history of Fowler's solution ingestion. Both of these groups included specimens of normal skin, epitheliomas (basal or squamous cell), keratoses (arsenical or senile),

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and Bowen's disease (intraepidermal squamous-cell epithelioma).

A total of 82 specimens (41 normal skins, 21 epitheliomas, 15 keratoses, and 5 Bowen's disease) were analyzed from patients with arsenic history. A total of 101 specimens (56 normal skins, 35 epitheliomas, 8 keratoses, and 2 Bowen's disease) were analyzed from patients with no arsenic history.

Method

The specimens were removed mostly by elliptical excision. Normal skin specimens usually consisted of the skin adjacent to the pathologic lesion, although in some patients normal skin from another part of the body was submitted. The sample was halved, one half was for histologic diagnosis, the other half for quantitative analysis at the Activation Analyses Group, Analytical Chemistry Division, Oak Ridge National Laboratory. A few specimens for analysis were halved again and each submitted under different identification numbers for the purpose of comparing values found. The specimens for analysis were placed in 10% chemically pure formalin fixative. With each lot of specimens submitted, a separate sample of the formalin fixative was included for determination of arsenic contamination.

The method of analysis was as follows: Each specimen was placed in a tared polystyrene tube in a vacuum desiccator. They were weighed at intervals until a constant weight was obtained. The specimens had a dry weight ranging from 2.9 mg. to 102.9 mg. Following this, the samples were irradiated in the Graphite Reactor for at least 16 hours. After the irradiation, each sample was placed in a distillation flask and decomposed in an acid mixture. Isotopic carrier was added and the mixture distilled to remove the arsenic carrier and radioactivity from the flask. The distillate was treated with hydrogen sulfide of scavenging "carriers" added to assist in the decontamination. The arsenic carrier was finally precipitated as arsenic metal to determine the chemical yield of each experiment and to provide a suitable form for counting. All radioactivity measurements were made in a Geiger-Müller counter. The comparator samples were processed in the same way.

Results

All of the following values for arsenic are micrograms per gram of tissue (dry weight). From the 27 patients with arsenic history there were 82 specimens quantitated for arsenic (41 normal skin, 21 epithelioma, 15 arsenical keratosis, and 5 Bowen's disease). From the 60 patients with no history of arsenic ingestion there were 101 specimens (56 normal skin, 35 epithelioma, 8 senile keratosis, and 2 Bowen's disease). For the arsenical history specimens, the median value in micrograms of arsenic per gram of tissue (dry weight) was normal skin 0.17 (range 0.01-3.50), epithelioma 0.10 (range 0.04-4.10), keratosis 0.26 (range 0.04-0.97) and Bowen's disease 0.11 (range 0.01-0.20). For the nonarsenic history specimens, median value was normal skin 0.10 (range 0.05-2.30), epithelioma 0.12 (range 0.02-0.84), keratosis 0.13 (range 0.01-0.72) and Bowen's disease, one 0.33 and the other 0.54 (Table 1).

The arsenic values in the various categories of specimens are shown in Table 2. A wide variation in the values were found within each group of lesions; however, throughout, the majority of values were within the 0.00-0.20 range. One patient with an arsenic history had 4.10 for the epithelioma, and the adjacent normal skin was 0.91; another epithelioma situated nearby on the lower back and excised at the same time contained 0.22 for the epithelioma and 0.40 for the adjacent normal skin, as shown in Table 3.

TABLE 1.—*Arsenic Values*

	Arsenic History				No Arsenic History			
	Normal	Epithelioma	Keratosis	Bowen's	Normal	Epithelioma	Keratosis	Bowen's
Specimens, no.	41	21	15	5	56	35	8	2
Median μg/gm.	0.17	0.10	0.26	0.11	0.10	0.12	0.13	
Range μg/gm.	0.01-3.50	0.04-4.10	0.04-0.97	0.01-0.20	0.05-2.30	0.02-0.84	0.01-0.72	

TABLE 2.—*Arsenic Values*

Arsenic μg/Gm.	Arsenic History				No Arsenic History			
	Normal	Epithelioma	Keratosis	Bowen's	Normal	Epithelioma	Keratosis	Bowen's
0.00-0.10	12	11	3	2	29	12	3	0
0.10-0.20	8	3	3	2	12	7	3	0
0.20-0.30	7	4	2	1	3	2	0	0
0.30-0.40	2	1	3	0	3	3	0	1
0.40-0.50	4	0	1	0	1	5	1	0
0.50-0.60	0	1	0	0	2	2	0	1
0.60-0.70	1	0	0	0	3	0	1	0
0.70-0.80	1	0	0	0	0	1	0	0
0.80-0.90	1	0	1	0	0	2	0	0
0.90-1.00	2	0	2	0	0	1	0	0
1.00-2.00	2	0	0	0	2	0	0	0
2.00-3.00	0	0	0	0	1	0	0	0
3.00-4.00	1	0	0	0	0	0	0	0
4.00-5.00	0	1	0	0	0	0	0	0
Total	41	21	15	5	56	35	8	2

A comparison between arsenic contents of epitheliomas and the adjacent normal skin showed that in the arsenic history group 12 of the 17 normal skin specimens contained more arsenic than their respective adjacent epitheliomas. In the group with nonarsenic history 10 of the 18 normal skin specimens contained more arsenic than their respective adjacent epitheliomas. See Table 3.

Wide variations in the amounts of arsenic occurred in the same patient. In one patient, 5 normal skin specimens had values of 0.15, 0.17, 0.40, 0.65 and 0.91; 4 epithelioma specimens had 0.22, 0.22, 0.31, and 4.10.

TABLE 3.—*Amount of Arsenic in Epitheliomas and that of the Adjacent Normal Skin*

Patient	Arsenic History		No Arsenic History	
	Adjacent Normal Skin	Epithelioma	Adjacent Normal Skin	Epithelioma
1	0.20	0.16	0.05	0.04
2	0.05	0.07	0.09	0.03
2	0.20	0.10	0.07	0.05
3	0.45	0.04	0.19	0.49
4	0.02	0.05	0.17	0.22
4	0.09	0.03	0.02	0.08
5	3.50	0.03	0.22	0.32
6	0.09	0.07	0.64	0.21
7	0.91	4.10	0.07	0.05
7	0.40	0.22	0.05	0.03
7	0.15	0.31	0.18	0.39
8	0.04	0.03	0.16	0.11
9	0.09	0.07	0.18	0.12
10	0.20	0.08	0.18	0.13
11	0.77	0.58	0.07	0.10
12	0.13	0.86	0.57	0.84
12	0.10	0.03	0.39	0.41
			0.59	0.46

In 11 patients with arsenic history 2 or more specimens of normal skin on different parts of the body, taken from the same patient, were assayed for arsenic. There was a wide range of values in specimens from the same patient. This was also true of multiple normal skin specimens from three patients with no arsenic history.

Comment

The neutron activation analysis method was found to be reliable for consistency in the amount of arsenic found on the basis of comparing 5 specimens which were halved. Each specimen was analyzed under a separate number. Each half of 3 specimens was reported with the same value and 2 had a variation of only 0.02μg. between identical specimens.

Five patients had multiple epitheliomas on the trunk typical of arsenical epitheliomas, but no history of arsenic ingestion could be elicited. In these cases there was no increased arsenic either in the normal skin nor in the epitheliomas when compared to the findings for the nonarsenic history patients.

The wide range of values in each category, as shown in Table 2, precludes the

possibility of any acceptable correlation between comparable normal skin or lesions of different patients.

Scott,[7] using neutron activation analysis for the quantitative determination of arsenic, had a number of findings differing from those found in this study. He reported the arsenic values in μg/gm. wet weight; this study reports the amount in μg. per gram dry weight. Therefore, comparison between these two studies for the actual amount of arsenic reported in the various specimens is not feasible. Scott[7] found more arsenic in epitheliomas than in other parts of the skin of patients with arsenic history; this present study showed more arsenic in the normal skin adjacent to the epithelioma in the majority of patients with or without an arsenic history. His values had a narrow range while this study showed a wide range. This difference may be due to the relatively small number of specimens he submitted to quantitation. This study does confirm Scott's findings that there is a tendency to increased amounts of arsenic in normal skin in patients with a history of arsenic ingestion.

This study confirms Osborne's findings that there is no relationship between the amounts of arsenic in the skin and the development of epitheliomas. Further, Montgomery and Waisman's findings, that there is less arsenic in superficial epitheliomas than in the normal adjacent skin is borne out by this study. However, their observation that arsenical epitheliomas contain more arsenic than the adjacent skin, is not confirmed by this present study.

Summary and Conclusions

The amount of arsenic was determined by neutron activation analysis in 183 skin specimens from 87 patients. Of these patients, 27 had a history of ingestion of potassium arsenite solution for therapeutic purposes and 60 had no history of arsenic ingestion.

From the data obtained it is believed that the following conclusions may be drawn:

1. Neutron activation analysis for quantitative measurement of trace amounts of arsenic in the skin is a reliable method.

2. In the majority of cases there is less arsenic in the epitheliomas than in the adjacent normal skin, not only in arsenical epitheliomas, but also in epitheliomas in persons without arsenic history.

3. There is a slightly greater amount of arsenic in the normal skin of patients with arsenic history.

4. There is no significant difference in the amount of arsenic between arsenical epitheliomas and epitheliomas in patients with no arsenic history.

5. The amount of arsenic in the skin seems to have no significant bearing upon the development of cancer.

6. The wide variation of the amount of arsenic found in the skin of those with or without a history of arsenic ingestion does not indicate arsenic quantitation as a diagnostic method.

Dr. Gerald F. Machacek determined the histological diagnoses of the specimens.

Mr. G. W. Leddicote performed the activation analyses of all the specimens at the Activation Analyses Department, Oak Ridge National Laboratory.

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ABSTRACT OF DISCUSSION

DR. EARL D. OSBORNE, Buffalo: Dr. Domonkos deserves commendation for applying a new research tool in dermatology. It is unfortunate that his findings had to be essentially negative. It was to be hoped that further knowledge might be elucidated regarding carcinogenesis. It is still possible that in the future the continued study of psoriatic patches by the use of this new method of neutron activation analysis will bring additional scientific facts.

When I read Scott's paper in the *British Journal of Dermatology* last year, it set me to thinking again about all of these cases of epitheliomata arising in patches of psoriasis where there is no history of arsenic ingestion or any increase in the quantitative deposition of arsenic in the area of skin involved. However, for every patient developing epitheliomata with no history of arsenic ingestion, there are at least 9 or 10 with a previous history of the ingestion of arsenic. What part does the arsenic play in the stimulation of the skin to develop epitheliomata, not only of the basal-cell variety but occasionally of the squamous-cell type? The most acceptable theory is that the arsenic acts in some way to stimulate the epidermis through its action on the sulfhydryl groups. This has not been proved.

I spent about eight years of my research life working on arsenic. Many thousands of sections and chemical determinations were made. Quantitative determinations were made with the old Marsh and with the modified Gutzheit methods. One could always demonstrate just as much arsenic in the surrounding skin as in the skin involved with epithelioma. In some unpublished material we took the curettings from quite a number of so-called arsenical epitheliomas including several good-sized lesions and submitted these curettings to quantitative arsenical determination. The determinations for arsenic were less than in the normal skin surrounding the epitheliomas.

As regards arsenical keratoses, we could always demonstrate microchemically and by the Gutzheit quantitative method an increase in arsenic in the keratoses.

It is probably true that arsenic under certain conditions should be considered a carcinogen. However, there are other important factors, such as heredity. This is probably the most important factor. The incidence of arsenical epitheliomata bears no relationship, generally speaking, to the quantity of arsenic ingested nor in general, to the amount of arsenic found in the skin. It is my opinion that active inflammatory reaction is a necessary adjunct, along with the arsenic, in the development of so-called arsenical epitheliomata. For instance, two years ago, we saw a young man, 28 years of age, who took Fowler's solution for a period of three years and developed arsenical keratoses and some mottled pigmentation. While under our observation, he developed an infected sebaceous cyst on the shaft of his penis and this later developed into a pyogenic granuloma. Rapidly, and under our observation, this developed into a squamous-cell carcinoma.

I hope that Dr. Domonkos will carry on with this method. I hope that he will apply this new research tool in the study of rare trace elements in the skin. It is very apparent from the work that has already been done that great progress in the study of the physiology and chemistry of the skin depends upon a further elucidation of the facts regarding trace elements.

DR. MARCUS R. CARO, Chicago: Dr. Domonkos has demonstrated well that in patients with a history of arsenic ingestion, the normal skin surrounding the epithelioma contains much more arsenic than does the epithelioma itself. I think that this is a finding that is entirely logical, and it is to be expected. The arsenic is deposited in the skin at the time of ingestion. Ten, fifteen, or twenty years later a carcinoma develops in the skin. Why should one expect that the carcinoma will have more arsenic than the skin into which the arsenic was originally deposited? After all, this is a neoplasm which is formed long after the arsenic was ingested, and it has no source of arsenic from which it can become saturated during its period of formation. I think this finding is logical, and I am not at all surprised by it.

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: I should like to say just about what Dr. Caro said, in slightly different words. If one may consider a keratosis or a carcinoma that has developed anew as a clone resulting from a somatic mutation, then one may expect the neoplastic clone to contain less arsenic than the epithelium from which it originated. The arsenic could, by hypothesis, damage genetic function, initiate neoplasia, and be absent from the resultant lesion.

I ask Dr. Domonkos how, for my information in particular, and, I expect, ours in general, when a tissue specimen was subjected to neutron bombardment and its resultant radioactivity was measured by the Geiger counter, does one distinguish the radioactivity due to arsenic from the radioactivity due to altered iron, sodium, potassium, calcium, magnesium, and trace elements?

DR. LEON GOLDMAN, Cincinnati: Dr. Domonkos' work is interesting to all who are working on cancer immunology. It points again to the fact that there is no direct quantitative relationship to the supposed or suspected carcinogen. His work also suggests the possibility that, in view of the studies by Chester Southam, we ought to determine the blood properidin levels in our patients

with multiple malignancies to see if that is one of the features which can help to explain the development of multiple malignancies in some of these patients and not in others.

Dr. Sulzberger also reminded me that we had tried to explain this deficiency of previous arsenic determinations in the malignancies and keratoses associated with it by trying to patch test these patients to potassium arsenite solution both in normal skin and in the keratotic and malignant areas. We wished to see if that would explain some of the reactions in terms of local hypersensitivity. This was, of course, impossible.

Dr. Hamilton Montgomery, Rochester, Minn.: I was very much interested in Dr. Domonkos' presentation on the newer techniques for analysis of arsenic in the skin. Back in 1941, when Dr. Waisman and I presented our observations on arsenic epithelioma, we found more arsenic in the tumor than in the adjacent normal skin. We were not in accord with the late Nelson Paul Anderson, that all, or most, superficial epitheliomatoses were of arsenic origin and that most of them were of basal-cell origin. In our experience, the arsenic epitheliomas on the trunk are usually moist and histologically reveal a squamous-cell carcinoma in situ with the phenomenon of individual cell-keratinization. These lesions do not have the thread-like border of the ordinary basal-cell superficial epitheliomatosis.

I wish to point out that one may have systemic manifestations from arsenic epitheliomas. One patient had received potassium arsenite solution for psoriasis and developed a squamous-cell carcinoma, Grade 3, on the sole of his foot with metastasis to the groin. It was quiescent for many years following radium; then he developed an intraurethral carcinoma, again with the phenomenon of squamous-cell carcinoma in situ with so-called Bowenoid changes. Ten years later he developed cancer of the lung, from which he died. The histopathologic picture remained that of a squamous-cell carcinoma with individual cell keratinization.

Dr. Anthony N. Domonkos (Closing): Thank you very much for your comments. Dr. Sutton's question is answered in the main paper. I hope that there will be no misunderstanding in regard to these findings. There is no doubt that ingestion of pentavalent inorganic arsenic in sufficient quantities may cause arsenical epitheliomas; however, according to this study it is not due to the quantity of arsenic that is deposited in the skin. For this reason additional evidence is available to demonstrate that chelating agents such as dimercaprol (BAL) are of no benefit in trying to prevent the development of more epitheliomas.

Phototoxicity, Photoallergy, and Photoskin Tests

OTIS F. JILLSON, M.D., and WILLIAM L. CURWEN, M.D., Hanover, N.H.

Heat, cold, trauma, and light are the physical agents concerned in the production of physical hypersensitivity. Physical hypersensitivity to light is the most important and the most common of the dermatoses caused by these physical agents. Light is the etiologic agent in polymorphic light eruptions, solar urticaria, contact photodermatitis, and endogenous photochemical dermatitis. Light is a major precipitating factor in certain cases of skin diseases associated with porphyria, psoriasis, pityriasis rubra pilaris, keratosis follicularis, pellagra, lupus erythematosus, acne rosacea, herpes simplex, xeroderma pigmentosum, keratosis, cancer, and keratoacanthoma.

For over a century the diseases produced by light have been studied, with a marked surge of interest over the last decade or two. Because of this, there are now certain fundamentals available, as well as basic equipment, for the study of light hypersensitivity. Application of these essentials, however, has not become routine office procedure for practicing dermatologists. All are well acquainted with such terms as photodynamic reaction, phototoxicity, photoallergy, and with those fundamentals related to skin diseases produced by light. However, there is still some controversy in their interpretations. Therefore, phototoxicity and photoallergy will be described again in detail. The simplicity and necessity for carrying out certain photoskin tests in all cases of light hypersensitivity will also be stressed.

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Phototoxicity

When a photosensitizing substance is located in the skin, usually in the prickle-cell layer, in the required concentration, and then exposed to those wave lengths of light contained in its absorption spectrum, a reaction should take place. Thus, there are two essentials for a phototoxic reaction: (1) a photosensitizer located in the epidermis, and (2) exposure to wave lengths of light absorbed by the photosensitizer in the epidermis. For example, if a 1% solution of sulfanilamide is injected into the skin of human subjects and these injected sites are then exposed to the wave lengths of light contained in the absorption spectrum of sulfanilamide, a reaction will take place in all individuals so exposed.[1] An erythematous reaction appears within hours, persists for some days, and leaves a residual hyperpigmentation. In other words, the clinical aspect of a phototoxic reaction is nothing more than an exaggerated sunburn. It is a quantitative reaction, and if the quantity of the two essential ingredients is great enough, blistering is produced. Clinically, however, only rarely are the chemical substances and the required wave lengths present in the proper amounts for a reaction to take place. Individual predisposition must be assumed to account further for the rarity of phototoxic reactions.[2]

In contradistinction to a photoallergic reaction, there is no refractory period, no incubation period of five days or more, and therefore no change in reaction time.

Clinical examples of a phototoxic reaction are sunburn, endogenous photochemical dermatitis, some cases of contact photodermatitis, and possibly cases of light hypersensitivity associated with porphyria.

Phototoxic reactions do not require oxygen and therefore are not photodynamic reactions. Furthermore, they are separated clinically by the fact that when a photodynamic substance, such as hematoporphyrin, rose bengal, or eosin, is injected in a human who is then exposed to the appropriate wave lengths of light, an urticarial reaction appears—not an exaggerated sunburn.[3,4] Thus, a photodynamic reaction requires oxygen for its completion, and its clinical response in man is a wheal.

Photoallergy

On testing the skin with light, in addition to the sunburn reaction, a second or delayed reaction may appear after an incubation period of several days. This reaction differs from a sunburn, not only in having a prolonged incubation period, but also in appearance, in that it may be urticarial, papular, or eczematous. Unlike a phototoxic reaction, there is no residual hyperpigmentation. On retesting, the reaction time is shortened to minutes or hours. The local testing by light may flare previously diseased distant areas. Photoallergic reactions have been successfully passively transferred.[1,4]

It will be noted that it was mentioned previously that a photodynamic reaction is an urticarial reaction, and that now it is stated that a photoallergic reaction may also be urticarial. How to separate the two? Of some help is the fact that in a photodynamic reaction there is *no* change in the reaction time and there is residual hyperpigmentation; whereas in a photoallergic reaction, there may or may not be a change in the reaction time and there is *no* residual hyperpigmentation. However, the indisputable separation of these two types of photourticarial responses is done by means of the reverse passive transfer test.[5] The skin is irradiated first, and the serum injected later. If the test is positive, the urticarial reaction is on the basis of a photoallergic reaction. A photodynamic substance will never produce a reaction when injected into skin previously irradiated, since it needs the light energy to be activated.

Of greatest clinical significance is the fact that a photoallergic reaction, unlike a phototoxic reaction, is not dependent on specific fixed wave lengths of light.[6] Erythema seems to be one of the important precipitating factors, and at times intense erythema is required. Therefore, a photoallergic reaction may be produced by alpha rays, the various erythema zones of ultraviolet light, or by a phototoxic reaction. When a phototoxic reaction acts as the stimulator for a photoallergic reaction, specific wave lengths are involved, of course, as previously discussed. From a review of the literature of approximately 50 cases of solar urticaria, it is suggested that abnormal phototoxic substances may be present in some of these cases. This is certainly true in those cases of solar urticaria produced by wave lengths of light greater than 3700 A. Visible light has no metabolic effect on normal skin; therefore, a photosensitizer must be present. If the urticaria is produced only by visible light, the passive transfer test is almost always negative.[7] If this test is positive, then the reverse passive transfer test is used to determine whether a photodynamic substance is present. The sunburn spectrum, being the most frequent cause of erythema produced by light, is therefore the usual precipitating factor in a photoallergic reaction.[8]

A working hypothesis is that light changes a substance which is normally present in the human skin, a proantigen, into an antigen; or, equally important, it makes a chemical, such as a drug present in the skin, antigenic; then, in susceptible individuals, antibodies are produced and an allergic reaction may take place.[9,10] Therefore, ultraviolet-absorbing chemicals such as sulfanilamide, oil of bergamot, chemical sun screens, etc., can produce both a phototoxic and a photoallergic reaction; the phototoxic, potentially in

all; the photoallergic, in the few susceptible individuals. Both light hypersensitive mechanisms may be present. Clinical examples of photoallergic reactions are polymorphic light eruption and solar urticaria.

The antimalarial drugs are useful not only in the treatment of photoallergic reactions, but also in the differential diagnosing of phototoxic reactions from those of photoallergic reactions. It has been shown that chloroquine does not interfere with the normal erythema and pigmentation produced by the sunburn spectrum of 2,900-3,200 A. Chloroquine and other antimalarials interfere with and prevent the delayed photoallergic reactions previously described.[11,12] Since chloroquine does not prevent sunburn, and since its absorption spectrum is above 3,200 A., its effect in preventing photoallergic reactions is not that of a sun screen. It does not simply absorb the causative wave lengths of light. One plausible postulation is that while the patient is taking chloroquine, the proantigen, or the chemical, is changed into an antigen, and there is no interference at this point; but in some unknown manner, the antimalarial drugs interfere with the reaction between the antigen and the antibody.

With these facts in mind, as would be expected, the antimalarial drugs are effective in the treatment of photoallergic reactions but not in the treatment of the nonallergic phototoxic reactions.

For completeness it is necessary to define the ultraviolet light erythema zones, because they are pertinent to this discussion.

There are three ultraviolet light erythema zones,[13,14] which are well represented by the following three lamps: the so-called cold quartz, the hot quartz, and the Wood's light.

The cold quartz has its maximum erythema at 2,537 A. After exposure, erythema appears in a few hours with its peak around 12 hours. The erythema fades in several days and marked desquamation follows. Pigmentation may appear in a day and be gone in a few weeks.

The hot quartz has its maximum erythema at 2,967 A. Its reaction is almost identical to the cold quartz lamp with three exceptions: blistering is more readily produced, desquamation is less, and the peak erythema is later—at about 24 hours. Although 2,967 A. is the most efficient wave length in producing erythema, with increased dosage, 3,131 A. is the wave length which intensifies the erythema and produces blistering.[14]

The Wood's light has its maximum erythema at 3,650 A. The erythema and pigmentation appear within minutes to an hour and may disappear just as soon, or the pigment may persist for months. Much more energy is required to produce this immediate erythema.[14]

Equipment

Certain basic equipment is required in order that the fundamentals just presented may be applied to a clinical problem of light hypersensitivity. In most sections of the United States, sunlight is not dependable. Since it is not predictable or controllable, it is not practical to use in testing even though it is what causes the skin disease. Exact measurements cannot be carried out nor any consistent data accumulated. Hot quartz lamps or cold quartz lamps have been used in the study of light hypersensitivity, but these lamps produce only a part of the wave lengths of light. They have the line-type of emission, not a continuous spectrum as is found in sunlight. A carbon arc source of light has a continuous spectrum of ultraviolet and visible light, and is far more satisfactory (Fig. 1). Because different wave lengths of light are involved in the various clinical forms of light hypersensitivity, it is necessary to have a few glass color filters to delineate wave length transmission from the carbon arc lamp (Fig. 2). A dermatologist's office equipment should include both a carbon arc lamp and glass color filters. Without this, or similar basic equipment, it is not possible to verify the exact diagnosis, or even to diagnose at all, some cases of light hypersensitivity. Further, this controlled form of light is of value in observing the course of the disease and in observing the response to therapy.

Photoskin Tests

There are two photoskin tests which are employed frequently in the study of light hypersensitivity: the minimal erythema dose (M.E.D.) and the delayed erythema dose

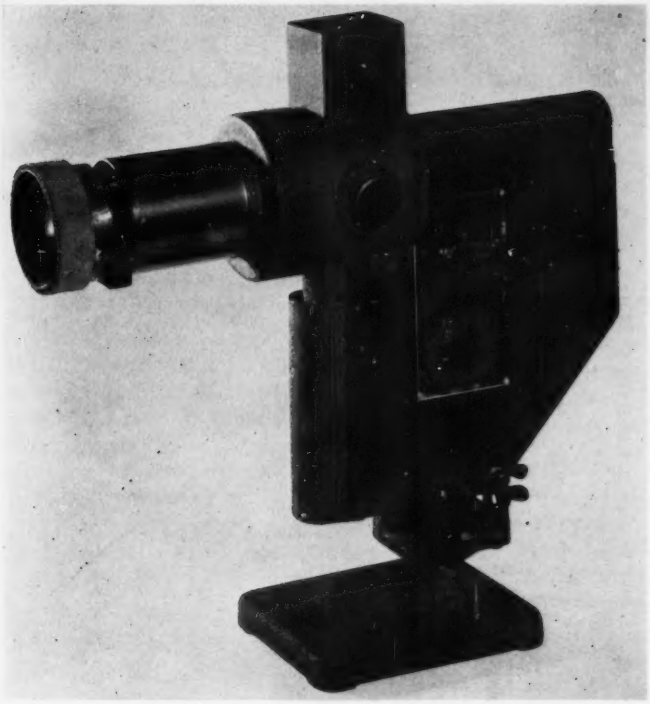


Fig. 1.—This is an efficient, versatile carbon arc lamp. It may be bought from the Bausch and Lomb Optical Company. A tube has been added to give a fixed distance from the light source to the skin (6.5 in.) and to provide a filter holder. National Carbon Company "Therapeutic B" carbons size 66 are used to produce a continuous spectrum of light.

(D.E.D.). These two tests will be described, interpreted, and applied.

Minimal Erythema Dose (M.E.D.).—The M.E.D. is determined on each patient. This is done for two reasons. With our equipment, if it is less than 30 seconds, it is abnormal (based on a study of over 200 patients). Secondly, it is necessary to determine the M.E.D. on each patient so that the delayed erythema dose can be determined.

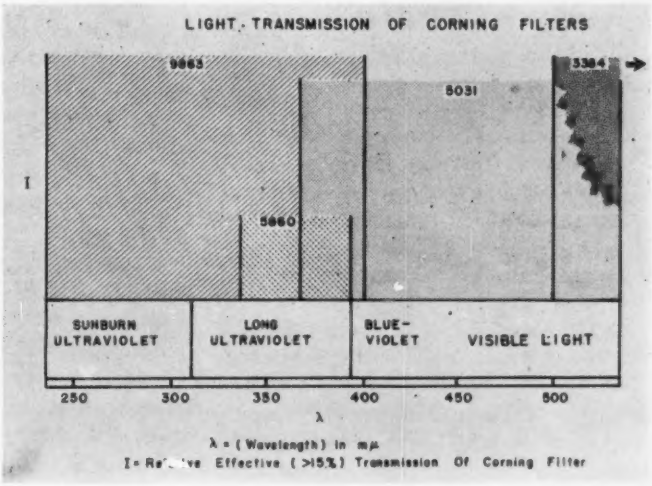


Fig. 2.—These four difference filters may be obtained from the Corning Glass Works, Corning, New York. These and single thickness window glass are the minimum types of filters required in the investigation of the various forms of light hypersensitivity.

CASES OF LIGHT HYPERSENSITIVITY

CASE	CLINICAL PICTURE	M.E.D.	SUNBURN THRU WINDOW GLASS	COMMENT
JC	EXAGGERATED SUNBURN	20	NO	TAKING CHLORPROMAZINE
LP	" "	20	YES	NO PROTECTION FROM PABA
JM	ECZEMATOUS TYPE OF P.L.E.	5	"	TAKING ANACIN
LM	"	10	"	SUNBURN FROM FLUORESCENT LIGHT
RH	"	10	"	TAKING ANACIN
AC	"	15	"	
BF	ERYTHEMA SOLARE PERSTANS	60	NO	CHLOROQUINE EFFECTIVE
JG	PRURIGO TYPE OF P.L.E.	45	"	" "
JS	" " " "	60	NOT DONE	" "
NS	" " " "	60	NO	" "
TJ	" " " "	45	"	" "
DM	PLAQUE-LIKE P.L.E.	15	NOT DONE	PARTIAL RELIEF FROM CHLOROQUINE
BS	" " "	15	NO	
VA	" " "	60	"	

Fig. 3.—P.L.E. refers to polymorphic light eruption. Sunburn through window glass refers to either clinical observation of this or to testing with the carbon arc light filtered through a piece of window glass.

The M.E.D., which is the minimal amount of light required to produce a barely perceptible erythema of the skin, is obtained as follows:

1. Clean the skin with acetone to remove contaminants and sweat. Human sweat absorbs wave lengths of light less than 3,300 A. and provides some protection against sunlight.[15]

2. Irradiate different areas of skin with increasing amounts of carbon arc light through the No. 9863 filter. This filter permits passage of the sunburn spectrum and absorbs many of the heat-producing infrared rays.

3. Read the irradiated areas 24 hours later to determine the M.E.D.

An abnormal M.E.D. (with our equipment less than 30 seconds) may be associated with the following data (Fig. 3):

A Phototoxic Reaction Represented Clinically by an Exaggerated Chronic Sunburn: This is usually associated with a history of parenteral exposure to certain drugs. There are many oral medications known to produce a hypersensitivity to sunlight. Most of the applicable investigative work has been done with the phenothiazine derivatives. A lowered M.E.D. has been noted frequently in patients medicated with these drugs.[16,17] Therefore, when the M.E.D. is abnormally low, all medicines ingested should be suspected, including both the obvious barbiturates and sulfonamides and the less obvious salicylates and coal tar derivatives (saccharin, acetanilid, and phenacetin).[18] Absorption from the lungs [19] and skin [20] should be kept in mind.

A History of Sunburn Produced by Wave Lengths of Light Above 3,200 A.[4]: These are the patients who are sunburned through window glass and by fluorescent light.[21-23] As a consequence of this, there is a failure of para-aminobenzoic acid (PABA) to prevent the exaggerated sunburn. Fifteen per cent PABA in a hydrophilic ointment has been proved consistently to be the best sun screen by both experimental testing and clinical usage.[15,24] However, since the absorption spectrum of PABA extends only to 3,200 A., it does not fully protect patients with lowered M.E.D. More protection is provided by adding a sun shade such as titanium dioxide (Solar Cream).[15] Since two of our patients had the M.E.D. reaction intensified at the PABA application site, it is necessary to test each sun protective prepa-

ration on the patient by this method before use.

The Eczematous Type of Polymorphic Light Eruption:[6,15,25,26] Four of our cases have M.E.D.'s in the range of 5-15 seconds. In these four individuals the eczematous photoallergic phase of this disease was controlled by chloroquine, but the phototoxic chronic sunburn phase was not.

The Plaque-like Polymorphic Light Eruption:[27] In two of our three cases with this disease, the M.E.D. is 15 seconds. That a certain number of these cases represent a combined phototoxic-photoallergic reaction may be surmised by quoting Lamb, "Several cases of plaque-like, light-sensitive eruptions have been cleared by treatment with chloroquine but they still have sunburn reactions in the light exposed areas of the skin." [23]

Delayed Erythema Dose (D.E.D.).—It is necessary to produce an intense erythema to activate certain photoallergic skin diseases. The characteristic pathological reaction, which is in part an erythema, does not evolve until after the appearance of the normal sunburn erythema resulting from the testing. This delayed erythema is obtained by giving a D.E.D., or delayed erythema dose, of ultraviolet light, as follows:

1. Apply 8 M.E.D. to the washed, untanned, normal skin. This amount is based on the experience of others [6,13] and on Blum's calculation that even under the most extreme conditions, no more than 20 M.E.D. unit of radiation falls on a person on a given day.[29]

2. Read the irradiated area for a period of seven to ten days.[6,13,29,30] The expected sunburn erythema will appear; as it is fading, around the third day, a second, more persistent erythema may appear. The diagnostic allergic reaction is then the appearance of papules (or eczematous reaction) within this zone of erythema. This papular reaction may not appear for seven to ten days, or it may be absent at the test site but appear on the distant diseased areas of the skin, or it may be necessary to irradiate previously diseased skin to evoke this papular response.[6]

The delayed erythema dose (D.E.D.) is applied in the testing of the following photoallergic diseases:

The Prurigo or Papular Type of Polymorphic Light Eruption: The M.E.D. is normal [11] but the D.E.D. produces a papular reaction in a certain percentage of these cases.[12] These are the cases that invariably respond to the antimalarial drugs.[31-33] In two of our four cases referred to in Figure 3, a papular response was produced by the D.E.D. However, in one of these two cases, it was necessary to irradiate a previously diseased skin site. This is a very common disease. This past spring we have seen eight additional cases, 50% of whom had a papular response following irradiation with a D.E.D.

Contact Photodermatitis: We are referring here to an entirely different clinical type of contact photodermatitis from the localized, bullous dermatitis with marked residual hyperpigmentation resulting from photocontact with oil of bergamot, lime oil, etc. This important new clinical type of contact photodermatitis was first described by Sams in 1955 as follows: "The dermatitis here is usually not limited to localized areas but involves more diffusely the exposed surfaces and is characterized by an eruption, which, in addition to erythema, may also show papular and papulourticarial lesions and the eczematous component seldom shows gross vesiculation." [2] (Fig. 4.)

Investigation of this type of contact photodermatitis requires use of photopatch tests, a technique wherein the suspected contactant is applied to the skin and irradiated.[17,34,35] Without this photopatch test, a confirming diagnosis cannot be made.

In our experience it is necessary to irradiate the patch test sites with both the M.E.D. and D.E.D. On the first day, patch tests are performed in triplicate to the suspected contactants. Tests are performed the same day to determine the M.E.D. Twenty-four hours later the M.E.D. is read, two sets of patch tests are removed, and the skin is cleaned with acetone. One set of the exposed tested sites is then irradiated with just less than the M.E.D., and the other exposed tested sites are irradiated with the

Fig. 4.—Contact photodermatitis from liquid make-up. The mild reaction is characteristic of many of these cases.

D.E.D. All test sites, including the control third set, are read at 48 hours and for several days thereafter, as discussed under the D.E.D. The details of this photopatch technique will be described in a future paper.[36]

Both phototoxic (Fig. 5) and photoallergic (Fig. 6) reactions may be present.

By using the combined method of photopatch testing, several cases of this type of contact photodermatitis have been diagnosed (Fig. 7).

Conclusion

In the diseases under discussion, the M.E.D. is used to test for phototoxicity. When the M.E.D. is lowered, there is a more intense, persistent erythema which may precipitate a superimposed photoallergic reaction, either of the plaque-like or eczematous type of polymorphic light eruption. (We have had no experience with solar urticaria.) A lowered M.E.D. is not altered by antimalarial drugs nor by local application of

Contact Photodermatitis

Case	Causative Agent	Phototoxic	Photoallergic
1	Compazine		+
2	Phenergan cream		+
3	Thorazine	+	
4	Noxzema	+	
5	Skol		+
6	Sunbath Lotion		+
7	Cuticura Ointment	+	
8	Geranium	+	
9	Hazel Bishop Liquid Makeup	+	+
10	Jergen's Lotion	+	

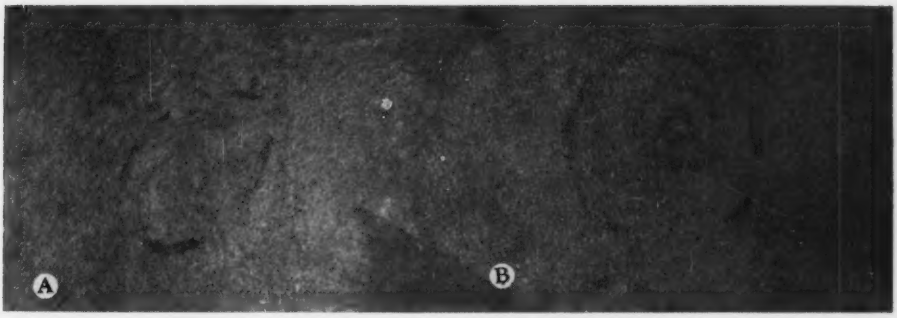
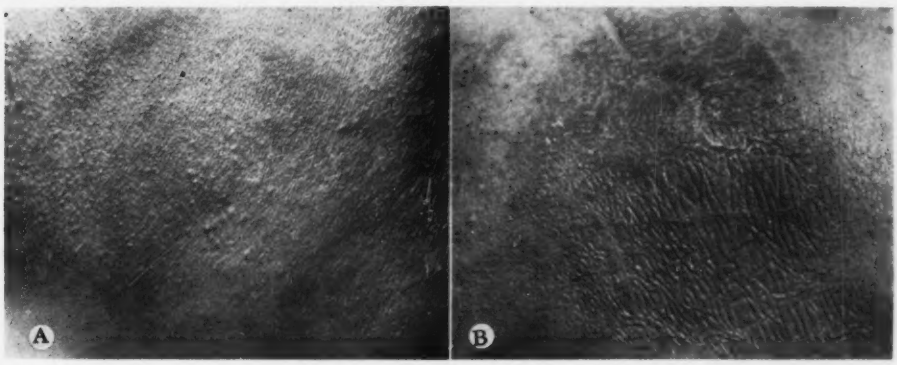


Fig. 5.—Positive photopatch test of the phototoxic type from Jergen's Lotion. Area *A* is the control. Area *B* was irradiated with just less than the M.E.D. as determined on this patient.

Fig. 6.—The two types of photoallergic reactions that may appear after irradiating the suspected photocontactant with the D.E.D.: *A*, the papular response, and, *B*, the eczematous response noted in the center of the irradiated area.



para-aminobenzoic acid. It may be associated with a sunburn through window glass.

When the M.E.D. is normal, as occurs in the prurigo type of polymorphic light eruption, it is necessary to use an intense erythema (D.E.D.) to precipitate the photoallergic reaction. This may also apply when testing some of the cases of contact photodermatitis where the M.E.D. irradiation of the suspected contactant on an area of noninvolved skin may not elicit a reaction. In these cases the contact photosensitizer produces a primary photoallergic reaction and is not secondary to a phototoxic reaction.

Summary

The phototoxic reaction, photodynamic reaction, photoallergy, ultraviolet light erythema zones, and the diagnostic use of antimalarial drugs have been discussed.

The minimal erythema dose and the delayed erythema dose produced by the carbon arc source of light have been described, interpreted, and applied to certain problems of light hypersensitivity.

Hitchcock Clinic.

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ABSTRACT OF DISCUSSION

DR. BEATRICE MAHER KESTEN, New York: Dr. Jillson is to be commended for reviving interest in the use of the carbon arc lamp in office practice and, through its use, adding to our knowledge of abnormal reactions to sunlight; also, for the alliterative title of his paper.

We are indebted to Stephan Epstein for classifying reactions as either phototoxic or photoallergic. As noted by Dr. Jillson, Epstein produced local exaggerated erythemogenic responses in all of his six volunteers with a solution of sulfanilamide. He proposed the name, phototoxic reaction, for this primary photochemical sensitization, and suggested that it might be due to photodynamic action. Ten days after the initial reaction, two of his volunteers developed wheals in the test sites. Further exposure to sunlight produced an accelerated response to whealing. Under the heading of photoallergic, he listed this latter response and also the response in the cases reported by Sams of localized photosensitization following contact with the oil of Persian lime.

Photodynamic action of sunlight was proposed by Tappeiner back in the Finsen era to explain all manner of photobiologic phenomena in terms of photosensitization by dyes and pigments. It grew out of his pupil Raab's discovery that paramecia swimming in a solution of acridine dye died when exposed to sunlight. If the dye was omitted or interposed between the paramecia and sunlight, they continued to swim. Extensive studies with dyes showed their absorption spectra and the action spectra in sunlight producing the reaction to be in close approximation, and that the reaction required molecular oxygen. Following this observation, investigators induced photochemical sensitization by the intradermal injection of dyes. The reactions were characterized by erythema, whealing, and, later, pigmentation. In some instances, systemic photosensitization occurred. Later, photochemical sensitization with dyes was produced deliberately as a therapeutic measure; for example, in increasing the erythemogenic response to sunlight in some skin diseases.

To turn now to antimalarial drugs, which, Dr. Jillson reasons, would be expected to be effective in the treatment of photoallergic and not phototoxic reactions, I should like to suggest that the reverse might be the case, for the following reasons: the absorption spectra of mepacrine, chloroquin, and camoquin correlate well with the action spectrum inducing the sunburn erythema. Ointments containing quinine, mepacrine, or chloroquin are effective chemical sunscreens. The chloroquin group has been reported as ineffective in the treatment of allergic skin diseases not produced by sunlight. I have not found them effective in the treatment of solar urticaria. They are, however, effective in the treatment of nonallergic eruptions, such as lupus erythematosus, which may be precipitated by light, and in the prevention of certain phototoxic reactions to sunlight.

In phototesting, Dr. Jillson has fitted his practical lamp with the therapeutic B or sunshine carbon. It contains metals of the cerium group and emits a practically continuous spectrum ranging from 2,000 A. well into the infra-red zone. As the object of phototests is to determine whether sunlight is related to the patient's symptoms, it might be well to use in the initial tests a Corex D filter rather than the Corning filter No. 9863. The latter transmits wavelengths between 2,000 and 4,000 A., and those below 2,900 are not present in ordinarily available sunlight. With the Corex D filter, wavelengths below 2,800 A. are screened out, and longer wavelengths known to cause eruptions are uninhibited.

If the skin reacts abnormally to the initial phototest, it is of therapeutic importance to know whether the reaction is produced by wavelengths inducing the erythemogenic response causing sunburn, i.e., wavelengths between 2,900 and 3,200 A. As Dr. Jillson has demonstrated, the spectrum which produces this erythemogenic response may be intercepted with filter No. 5860, or one may use a piece of greenish window glass. If no reaction follows this test, one may assume that protection is to be had by the topical application of the so-called chemical sunscreens. As noted, a rough approximation of other wavelengths in sunshine which produce abnormal reactions may be ascertained by interposing other light-transmitting filters. Sharp delineation of the action spectra producing abnormal skin reactions is to be had by the use of other types of generators, usually outside of office hours.

By means of photopatch tests with ultraviolet light, Dr. Jillson has found an exaggerated erythemogenic response in patients with polymorphic light eruptions of the eczematous and plaque-like types, in photocontact dermatitis, and in two patients at the application site of PABA ointment. By increasing the exposure time, he has duplicated the papular response in patients with prurigo-like light eruptions and photocontact dermatitis.

I am much interested in the two patients in whom the minimal erythema dose was lowered by the application of PABA ointment. As they were in the group reacting to wavelengths beyond that which produces sunburn, one would not expect protection from the application of PABA, but neither would one expect an increased erythema. In testing some 200 patients with a variety of chemical sunscreening agents, including 15% PABA ointment, we noted no lowering of the M.E.D. When one thinks of the millions of people who use sunscreening agents each summer and the paucity of photosensitizations reported, the necessity of testing each patient with sunscreening agents before prescribing them appears doubtful.

Abnormal erythemogenic responses following phototests require careful interpretation. There are the problems of persistent vascular response to ultraviolet; of photoreactivation; of inhibition of re-

actions by exposure to longer wavelengths, and the frustrating variability of response to ultraviolet at different times in different individuals.

The distinction between phototoxic and photoallergic reactions in skin diseases is not determined, in my mind, by the lesions produced in phototesting nor by the spectrum which produces the reaction. Rather, it comes through correlation of the phototests with the patient's history and symptoms and by establishing whether or not the classical requirements of allergy are fulfilled.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I think that Dr. Jillson has given us a well-documented presentation of photosensitivity, which is of great practical value, especially in two respects: first, by his recommendation of the carbon arc lamp, because this is probably a better source for testing of light sensitivity than the quartz lamp which most of us use for this purpose; and, secondly, by the introduction of the concept of the "delayed erythema dose." He produces this delayed erythema dose by giving about eight times the "minimal erythema dose." His technique may explain why many of us, in our experiments with photosensitivity, have had so often negative results, because by giving only a minor or moderate erythema dose, we probably did not apply enough light.

On this occasion, I would like to comment on the use of the terms "photodynamic" and "phototoxic" reactions. I believe these terms should be used synonymously. I doubt whether Blum was justified in restricting the term, photodynamic, to those phototoxic reactions which require the presence of molecular oxygen. The term, photodynamic reaction, was coined by Raab and Tappeiner; they used it for the detrimental action of the combined effect of light and chemicals on paramecia, without reference to the utilization of molecular oxygen. The present confusion can be illustrated by the example of sulfanilamide. It has definitely been shown that sulfanilamide is a photodynamic drug when tested against paramecia. However, according to Blum's definition, when tested on the human skin, sulfanilamide would not be a photodynamic agent. I think it will only lead to artificial difficulties if we try to make a distinction between the terms phototoxic and photodynamic.

I would like to ask a question of Dr. Jillson. He spoke about the excessive sunburn reaction. There are patients who become excessively sunburned, especially the red-headed person. But, I do not believe the term of excessive sunburn can be applied correctly to Dr. Jillson's patient with an acute dermatitis of the ears, who became aggravated when he was exposed to sunlight through window glass. That means an excessive reaction to ultraviolet longer than 3,200 A., to a form of light which is not responsible for the sunburn. I wonder whether Dr. Jillson thinks this is just an excessive sunburn reaction, or whether he has any idea of an underlying photoallergic mechanism in this case.

DR. RUDOLF L. BAER, New York: It is obvious that, because of the photosensitizing action of some of the newer drugs, tests for phototoxic and photoallergic sensitivity are becoming increasingly important. I would like to ask Dr. Jillson whether he has had the opportunity to test patients with photosensitivity produced by chlorothiazide (Diuril). Dr. L. C. Harber, Dr. A. M. Lashinsky, and I have studied several patients with eruptions due to photosensitivity produced by chlorothiazide and hydrochlorothiazide (Hydrodiuril). In our tests we have used a carbon arc lamp with a Sunshine Carbon in addition to natural sunlight.

Progress is apparently being made in elucidating certain photosensitive eruptions from the biochemical viewpoint. Kimmig et al. (Ztschr. physiol. Chem. 311:234, 1958) isolated *N*-β-indolyl-3-acryloylglycine in the urine of persons who have been exposed to sunlight. Wulf (Arch. Dermat. u. Syph. 197:209, 1954) has reported that the difference between patients with polymorphous light eruptions and other persons is that those with polymorphous light eruptions have developed a photoallergic sensitization to this compound. He has attempted to demonstrate this experimentally by techniques which are very similar to those used by Dr. Jillson, and also by our group.

DR. JOHN H. LAMB, Oklahoma City: In Oklahoma, we are constantly working on this problem of light testing. Most of our cases come in at the busiest season of the year, that is, April to September, and perhaps we are not too accurate in our observations, but we are very discouraged as to reproducing any clinical lesions of the common type; namely, the plaque-like eruption. This eruption, we feel, must be due to repeated exposures to sunlight, plus scratching, plus infection, and cannot be produced in one or two five-minute tests. However, in several instances, we have, we feel, observed pathologic sunburn reactions in these plaque-like cases.

The urticarial eruptions to both the short and long ultraviolet rays, and to blue-green light, have been successfully reproduced.

Lastly, the two cases of the rare type, namely, the eczema-like or eczematous type: Both received small doses of ultraviolet light, and within 24 hours were hospitalized with an acute exacerbation of the disease, in the first, in the light-exposed area, and in the second, a generalized erythroderma developed. We have reported this, but we would like again to caution our members of the dangers of light testing in this rarer type of solar dermatitis.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: In pointing out the distinguishing features of these

varied photoreactions, and, particularly, in outlining the details of simple tests for photosensitivity, the author performs a valuable service. The emphasis on a carbon-arc source of light for testing is especially important. The selection of the site for testing, whether on the exposed or the unexposed skin, may also be significant. In some cases, repeated testing of the same site may be required in order to produce a reaction. Even so, I am frequently disappointed by the results of testing in cases where the clinical picture clearly indicates that photosensitivity exists.

Photosensitizing substances may fluctuate from time to time and may be diminished or absent at the time of testing. This may be the situation in cases of lupus erythematosus, porphyria, and in certain instances of vernal hydroa in childhood. Abnormal metabolites may be produced from normal dietary ingredients under special circumstances. Clare of New Zealand found this to be true in strains of susceptible Southdown lambs, who became sensitive to the sun as soon as chlorophyll was added to the diet.

Finally, photosensitivity may occur, not because of some factor which has been added or altered, but because of something which has been taken away, a lack or a failure of the defense mechanism. This is true in the case of albinos, certain blonds, and red-headed, freckled individuals who are often extremely susceptible to normal exposures to sunlight.

DR. OTIS FIELD JILLSON, Hanover, N.H.: I want to thank all the discussers, and attempt an answer to some of the questions.

Various delineating filters may be used to perform the photoskin tests under discussion. The important thing is to standardize your particular equipment so that an abnormal minimal erythema dose and the delayed erythema dose can be computed.

Dr. Kesten brought up the fact that in the paper I mentioned that there were two individuals in whom, after local application of para-aminobenzoic acid, the sunburn reaction was intensified as compared to the control. This was initially a surprise to me, but I think the answer might be that for any reaction to take place, there must be an absorption of wave lengths of light, and then once the wave lengths of light are absorbed, they are converted into longer wave lengths of light. Since both of these individuals had lowered minimal erythema doses, they could be sunburned by wave lengths of light above 320 mμ. Therefore, although para-aminobenzoic acid is effective in preventing sunburn in people with a normal sunburn spectrum, this is not true in patients with lowered minimal erythema doses as there is more light available to produce a reaction due to the conversion factor.

The questions of Drs. Epstein, Brunsting, and Baer are somewhat related. We believe also that something has been added, and that this addition is usually a drug. Certainly chlorothiazide is a good example. These are the patients who have lowered minimal erythema doses. If only this phototoxic phase is present then the antimalarials are ineffective, but this phototoxic reaction may precipitate a superimposed eczematous response. Chloroquin is successful in preventing this photoallergic eczematous phase.

Once again I thank the discussers.

Primary Irritation of the Skin

Observations on Threshold Reactions

JOHN B. HAEBERLIN Jr., M.D., and JACK M. FOX, M.D., Chicago

The importance of primary irritation of the skin in producing an eczematous dermatitis by itself, as well as influencing the engendering of an allergic eczematous contact dermatitis is well documented. The recent literature is replete with articles adding to the fund of observations on mechanisms of pathogenesis of the eczematous sensitization and various aspects of dermatitis and eczema, but relatively few references are found under the heading of primary irritation as such. At present much of this information is found under such topics as contact dermatitis due to specific agents, thermal injuries, industrial dermatitis, and eczemas of various sorts, and it is inseparably linked with studies on allergic reactions in the skin. This is quite understandable since the need for such a term arose from the introduction of the concept of allergy which called for a designation to distinguish allergic from nonallergic forms of reaction. Other existing terms such as "toxic" or "pharmacologic" do not quite fill the bill since they do not exactly connote nonallergically produced irritation. Information on primary irritation of the skin might well be brought together in a monograph for convenience and help in understanding this rather basic subject particularly for those entering into the study of this phase of dermatology without having grown up with it. It is the purpose of this paper to outline the scope of what is meant by primary irritation of the skin and to report some experimental observations on certain threshold reactions.

A primary irritant has been defined by Sulzberger [1] as "an agent capable of producing gross reaction without the necessity of a previous sensitization having taken place." It would follow that primary irritation would be any irritation produced by other than a previous sensitization (or allergic) mechanism. One is cause, the other effect. Yet primary irritation is often referred to as a more or less specific reaction in the skin mainly to be differentiated from an allergic eczematous contact dermatitis rather on theoretical than on clinical morphologic grounds. Since this is a much more restricted use of the term than the quoted definition it might be worth while to consider this apparent discrepancy in greater detail. What is meant by the terms Primary Irritant and Primary Irritation? According to accepted definitions the tables suggest what might be included under these terms.

It has been said that usage determines the meaning of words and the correctness of their application. If this is true we may expect meanings to change by an evolution-

TABLE 1.—*Types of Primary Irritants*

Physical	Chemical	Biologic
Friction	Acids	Endotoxins
Laceration	Alkalies	Exotoxins
Pressure	Solvents	Organisms
Heat	Oils	
Cold	Detergents	
Wet	Soaps	
Foreign body	Alkaloids	

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TABLE 2.—*Types of Reaction to Primary Irritants*

Vascular	Humoral	Cellular	Combined
Erythema	Edema	Epithelium	Necrotic
Urticaria	Electrolytes	Endothelium	Bullous
Triple response	Hormonal effects	Connective Infiltrate	Eczematous
	Pharmacologic		Granulomatous

ary process. It would appear that currently the term Primary Irritant is often used in the inclusive sense so that any of the examples in the table might be meant. On the other hand, unless otherwise designated a primary irritant reaction usually refers to an eczematous one. In the interests of accuracy and clarity this point seems worthy of emphasis for it may be misleading to think of primary irritation as a homogenous reaction type resulting from any nonallergic reaction in the skin so long as the stimulus is met with in adequate concentration. Certainly the more we work with these forces and reactions the more aware we have become of their differences. Is a mild erythematous reaction with triple response to an appropriate physical stimulus different only in degree from the lichenified eczematous response produced by prolonged friction? Furthermore, certain primary irritant chemicals behave differently both qualitatively as well as quantitatively when applied in varying concentrations to the skin. Compare graded dilutions of phenol with similar applications of an alkali. The initial reactions are very different in appearance and sensation yet appropriately applied both might yield an eczematous dermatitis without the intervention of an allergic mechanism.

Theoretical mechanisms relating to the interrelations between primary irritant and allergic eczematous reactions have recently been thoroughly discussed by Rostenberg [2] and his bibliography is entirely complete. However, it seems that so much remains to be learned about these subjects that it is well to avoid any rigidity in our thinking in this area. The table is intended only as a summary of interesting aspects of this type of inflammation as an aid in keeping the whole problem in mind while considering in detail only a small facet of it.

From a practical viewpoint factors influencing primary irritant reactions are numerous and interrelated so that one cannot always clearly separate those influencing the irritants from those influencing the reactions and the factors which might be crucial for one type of irritant may be of minimal importance for another. Because of the complexity of these factors it seems useful to classify the many types of observation under the following arbitrary headings which are considered appropriate for much of the reported work on this subject.

Factors Influencing Primary Irritants and Their Reactions

1. *Type of Irritant and Concentration or Intensity of the Stimulus.*—(Acids and alkalies may be met predominately by one function of the skin, heat or friction another, solvents another, etc. The effects of duration or cumulation of exposure and occlusion on primary irritant reactions.)

2. *Genetic Factors.*—(The influence of race, sex, pigmentation, neurovascular in-

TABLE 3.—*Mechanisms of the Eczematous Reaction*

Eczematous Stimulus	Mediators	Reaction Components	Eczematous Lesions
Primary irritants	Histamine	Epidermal cells (living & dead)	Edema with spongiosis
Chemical	Serotonin	Connective tissue cells	Vascular alterations
Physical	Heparin	Mast cells	Cellular infiltrate
Biologic	Leukotaxin	Cellular infiltrate	Acanthosis
	Other	Enzymatic interference	
Allergens		Dermal epidermal integrity	
Preformed		Vascular responses	
Haptens		Humoral osmotic and pharmacologic	

stability, as well as specific idiosyncroses on skin irritability.)

3. *Anatomic Localization on the Skin.*—(The influence of the stratum corneum, presence of follicles, sweat glands and sebaceous glands on the reactions of the skin to primary irritants.)

4. *Loss of Integrity Through Previous Irritation or Injury.*—(The effects of friction, pressure, defatting, maceration, buffering function, sweat retention, heat and cold, and chapping on irritability of the skin.)

5. *Influence of Disease and Drugs on Primary Irritant Reactions.*—(The effect of "eczemas," metabolic disturbances, neurovascular factors, etc. on the irritability of the skin.)

Many observations have been reported that can be classified primarily under one or another of these headings, but it is not to be supposed that these are really separate categories, for in a given case the sum of all the factors are operating. However, some experimental observations may be such as to allow certain factors to be constant, leaving a limited number of variables for comparison and consideration. Clinical dermatologists all make daily observations on one or a combination of these factors and use their impressions incompletely to explain the clinical kaleidoscope. The adage that "eczema begets eczema" and the well-known tendency of this type of inflammation to self-perpetuation are explained in part by autosensitization. But excluding allergic mechanisms what is the influence of primary irritation on the threshold to further primary irritation of the same and other skin sites? This facet seemed worthy of further study and we herewith report some simple investigations in this area.

Experiment A: A Study of the Influence of Massive Primary Irritation Dermatitis on the Threshold of Reaction to Primary Irritants of Uninvolved Skin and on the Skin at the Same Site After Apparent Healing

It was determined that croton oil and chrysarobin could be serially diluted to yield a fairly evenly graded inflammatory response on the clipped skin of guinea pigs when applied in controlled fashion. These chemicals were selected because they have both been shown to produce an *eczematous* response in sufficient concentrations and possess relatively little sensitization potential. Both irritants were diluted in mineral oil in the following concentrations:

	(1)	(2)	(3)	(4)	(5)
Croton oil (U.S.P.)	0.5%	1%	2%	3%	4%
Chrysarobin (tincture)	0.2%	0.4%	0.6%	0.8%	1%

(Extract of 1% Chrysarobin in hot oil was used as the 1% solution)

All guinea pigs were previously unused young albino males weighing from 250 gm. to 450 gm. at the start of the experiment. After clipping the fur from the back of the animals with a #2 Oster clipper the skin was wiped once with acetone to permit easy and intimate contact of the oily substances with the skin. Blotting paper in which uniform sized holes had been made ¼" in diameter was held firmly against the skin to pick up any excess of material as with a stencil. The irritants were applied as a drop by means of a smooth glass rod as nearly identically as possible in all cases. Reactions were read at 24 hours and any erythema present at this time was considered one plus, deeper erythema 2 plus, erythema with scaling 3 plus, erythema with oozing and crusting 4 plus. As a control against this being interpreted as a histamine type of vascular response and to observe any gross changes in vascular response due to the other procedures histamine was injected intradermally in concentrations of 1:10,000, 1:100,000 and 1:1,000,000 initially and at the time of each subsequent test application. Immediately after making the initial 24 hour reading this side of the guinea pig was liberally painted with 40% croton oil to produce a severe dermatitis over the entire side of the back. Three days later, at which time the inflammation had reached its height, the opposite side of the back was clipped, wiped once with acetone and the same dilutions of

croton oil and chrysarobin were applied and read at 24 hours. Finally, from 3 to 5 weeks later when the visible evidence of dermatitis had subsided on the side of the back so damaged, the dilutions of irritants were applied again in the same fashion to both sides for comparison. The stepwise procedure is outlined and the results are recorded in tabular form.

Steps in Determining the Threshold of Primary Irritation to Two Irritants Before, During, and After a Massive Irritation of Guinea Pigs' Skin

1. The right side of each guinea pig's back was clipped and wiped once over with acetone and graded dilutions of croton oil and chrysarobin in mineral oil were applied as uniformly as possible through identical holes in blotting paper.

2. The graded applications were read at 24 hours.

3. Immediately following this, 40% croton oil was liberally applied to this side of the back.

4. After 72 hours when the whole right side of the back was showing a four plus reaction the left side was clipped, wiped once with acetone, and the same test applications of croton oil and chrysarobin were applied as identically as possible.

5. After 24 hours the above applications were read and recorded.

6. In 3 to 5 weeks when the gross evidence of dermatitis had largely subsided the entire back was clipped and applications of the graded dilutions were again made to each side of the back.

7. Twenty-four hours later these test applications were read and recorded.

Controls Included:

1. Applications of mineral oil which was used as the vehicle for diluting the primary irritants.

2. A number of animals were given no application of the 40% croton oil but otherwise treated identically.

3. Histamine injections were made intradermally in 1:10,000, 1:100,000, and

TABLE 4.—*Effects of Croton Oil and Chrysarobin*

	Croton Oil				Chrysarobin			
			After Healing				After Healing	
G. Pig No.	Initial Test	At Height of Reaction	Irritated Side	Control Side	Initial Test	At Height of Reaction	Irritated Side	Control Side
1	133	633	233	475	325	1,031	491	525
2	210	310	625	675	0	783	100	716
3	316	525	641	1,025	1,033	1,258	841	425
4	425	525	225	825	641	1,091	591	425
5	191	375	108	133	0	866	100	100
6	133	316	108	225	491	616	0	200
7	108	325	275	275	225	616	0	425
8	625	1,025	216	1,025	1,258	1,758	783	200
9	166	725	316	425	491	1,133	225	0
10	341	725	216	725	425	1,425	450	300
11	191	525	125	925	591	1,258	841	425
12	58	316	325	925	0	616	391	300
13	225	725	225	625	391	1,008	325	300
14	233	725	325	725	0	1,091	200	300
Mean	239	555	283	643	448	1,039	381	331
			No Irritant				No Irritant	
15	725	341	316	525	1,208	591	225	300
16	425	516	425	516	741	416	616	125
17	216	316	108	525	491	783	225	200
18	175	225	83	225	225	391	0	391
19	58	325	225	725	0	450	0	425
Mean	320	344	231	503	533	526	213	288

1:1,000,000 dilutions initially and at the time of each test application to show that these vascular reactions were transient as compared to the primary irritant reactions and that they were not grossly altered by the production of the massive irritation.

4. Biopsies were taken for microscopic evaluation of the skin after apparent gross healing as compared with the control site.

The results of this experiment are recorded in Table 4. In order to express numerically a value to include not only the intensity of reactions but the concentrations at which such reactions occurred, we define as an Index of Irritation the sum of reaction intensities divided by the concentration of the irritant used for each reaction and multiplied by 100 to clear the decimals. This might be expressed symbolically:

$$\text{Index of Irritation} = \frac{R^1}{C^1} \times 100 + \frac{R^n}{C^n} \times 100$$

where R is the intensity of reaction from 0 to 4 plus and C is the concentration of the primary irritant in question and n is the number of reacting patch tests in a given set of conditions. For example, guinea pig 15 reacted to croton oil 3 plus at 4%, 3 plus at 3%, 3 plus at 2%, 2 plus at 1%, and 1 plus at 0.5%. The Index of Irritation was calculated as given on the bottom of this page. This is, of course, an arbitrary definition and the numerical value has only relative significance.

In comparing the mean Index of Irritation initially (239) with that at the height of reaction (555) it would appear that there was an increase in the Index after treatment of the opposite side. This was statistically significant according to both the Sign test [3] and the Rank test.[4] This finding was observed for both croton oil and chrysarobin and in the control animals where no massive irritant was applied this increase in the Index was not observed.

When making paired comparisons between the irritated side and the untreated side, no such consistent observations could be made. For croton oil the mean index of the control side (643) was higher than for the healed side (283) and this was significant by the Rank and Sign tests but for chrysarobin this was reversed and insignificant statistically. Furthermore, the Indices in the control groups were inconsistent. We are, therefore, unable to draw any conclusions from the data from this phase of the experiment. In interpreting these results we must bear in mind that the guinea pigs used were relatively young and were three weeks older when retested than at the time of initial testing.

Experiment B: The Influence of Ultraviolet Irradiation and Stripping of the Stratum Corneum on the Threshold of Primary Irritation of the Skin

This study was done on ten white male students between 22 and 27 years of age and one of 49 years. The primary irritant used was Tr. cantharides (N.F.) in concentrations of 30%, 20%, 10%, and 5% in ethyl alcohol and pure ethyl alcohol was used as a control. This substance was chosen because it was found to produce a fairly uniform response in the skin of various persons and is accepted as a primary eczematous irritant with a low index of allergenicity. As a source of ultraviolet light we used a hot mercury quartz lamp (Hanovia Alpine Luxor model). The procedures were carried out in the following stages:

1. The right flexor forearm was irradiated for 20 seconds at 30 inches—a dose known to produce a mild erythema in most persons.

2. Immediately after the above exposure the series of dilutions of Tr. cantharides was applied as patch tests to the flexor aspects of both forearms. These were made of a uniform circular piece of white blotting paper ¼" in diameter and just saturated with the solutions for testing. They were held in place by Scotch tape strips for

$$\frac{3}{4} \times 100 + \frac{3}{3} \times 100 + \frac{3}{2} \times 100 + \frac{2}{1} \times 100 + \frac{1}{0.5} \times 100 \text{ or } 725.$$

TABLE 5.—*The Influence of Ultraviolet Irradiation and Stripping of the Stratum Corneum on Reactions to Graded Concentrations of Tincture of Cantharides**

Subject	Tr. Cantharides and Ultraviolet Right Arm (A)						Tr. Cantharides Alone Left Arm (B)						Ultraviolet Light—Irradiated Right Arm										Unirradiated Left Arm									
													Stripped (C)						Unstripped (D)				Stripped (E)						Unstripped (F)			
	0%	5%	10%	20%	30%	0%	5%	10%	20%	30%	0%	5%	10%	20%	30%	0%	5%	10%	20%	30%	0%	5%	10%	20%	30%	0%	5%	10%	20%	30%	0%	5%	10%	20%	30%
1	0	0	0	1+	0	0	0	0	3+	1+	0	0	0	0	3+	0	0	2+	0	0	0	0	1+	2+	4+	0	0	0	0	4+	0	0	0	4+
2	0	0	0	0	0	0	0	0	0	0	0	0	0	1+	1+	0	0	0	0	1+	0	0	1+	4+	4+	0	0	0	0	4+	0	0	0	4+
3	0	0	0	2+	3+	0	0	0	0	2+	0	0	0	4+	4+	0	0	0	0	1+	0	0	1+	4+	4+	0	0	0	0	1+	0	0	0	4+
4	0	0	0	2+	3+	0	0	0	0	3+	0	0	0	1+	4+	0	0	0	1+	3+	0	0	1+	3+	4+	0	0	0	0	1+	0	0	0	4+
5	0	0	0	0	1+	0	0	0	0	0	0	0	0	1+	1+	0	0	0	0	0	0	0	1+	1+	4+	0	0	0	0	2+	0	0	0	2+
6	0	0	0	0	3+	0	0	0	2+	3+	0	0	0	1+	1+	0	0	0	0	2+	0	0	0	1+	4+	0	0	0	0	0	0	0	0	0
7	0	0	0	1+	4+	0	0	0	0	1+	0	0	0	1+	1+	0	0	0	0	1+	0	0	0	0	1+	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	2+	0	0	0	0	4+	0	0	0	1+	1+	0	0	0	0	1+	0	0	0	0	1+	0	0	0	1+
9	0	0	0	0	3+	0	0	0	0	2+	0	0	0	0	4+	0	0	0	2+	2+	0	0	0	0	3+	0	0	0	0	3+	0	0	0	3+
10	0	0	0	1+	4+	0	0	0	0	4+	0	0	0	0	4+	0	0	0	1+	4+	0	0	1+	1+	4+	0	0	2+	2+	3+	0	0	2+	3+
11	0	0	0	1+	1+	0	0	0	0	0	0	0	0	1+	2+	0	0	0	0	0	0	0	1+	2+	4+	0	0	0	0	1+	0	0	1+	1+

* Original Readings.

its occlusive effect but the apposition and adherence were not entirely satisfactory.

3. The above patch tests were removed after 24 hours and read immediately and recorded. Reactions were graded from 1 to 4 with a minimal erythema as 1, intense erythema 2, erythema with vesicles or scaling as 3, and bullous reaction as 4.

4. For the next four weeks the right flexor forearm was exposed to the ultraviolet irradiation nearly every day to approximate the type of exposure used by Miescher so that we could expect the type of response reported by him.[5]

5. After this preparatory irradiation corresponding areas of the two forearms were stripped by the application and removal of Scotch tape repeatedly as described by Pinkus.[6] Ten strippings were arbitrarily used because in preliminary trials it was found that when 20 strippings were done some unduly severe reactions were encountered, and it was felt that the removal of 10 layers of keratin would be significant and safe.

6. Immediately after the stripping the same graded concentrations of Tr. cantharides were again applied as patch tests to stripped and unstripped areas in irradiated and unirradiated skin in as nearly identical fashion as possible, care being taken to avoid the sites of previous applications. The hair was clipped so that it would not interfere with the apposition of the patches.

7. Twenty-four hours later the patch tests were removed, reactions read and recorded, and on three persons biopsy specimens were taken from five areas: (1) normal skin from center of left flexor forearm; (2) similar site on irradiated area of right flexor forearm; (3) site from stripped skin of right arm; (4) site from stripped area of left arm, and (5) a moderate erythematous reaction.

In interpreting the reactions it was felt that both the concentration of the irritant and the intensity of the reaction should be considered. In Table 5 the readings are recorded as one to four plus in intensity for

TABLE 6.—*The Influence of U.V.L. and Stripping on Threshold Reactions to Primary Irritation*

Case	U.V.L. + Tr. Canth. (A)	Tr. Canth. Alone (B)		Irradiated		Unirradiated	
				Stripped (C)	Unstripped (D)	Stripped (E)	Unstripped (F)
1	5	18	4 weeks irradiation	10	20	33	13
2	0	0		8	3	93	13
3	20	6		43	13	43	3
4	20	10		18	10	25	8
5	3	0		5	0	8	23
6	20	20		8	6	18	6
7	18	3		8	3	3	0
8	0	6		13	30	3	0
9	10	6		13	6	10	15
10	40	33		13	18	148	83
11	8	0		11	0	213	8
Mean	13	9		14	10	54	16

* Table converted to values for Indices of Irritation.

† Index of Irritation $= \Sigma\left(\frac{\text{reaction intensity}}{\text{concentration of irritant}} \times 100\right)$

each graded concentration patch applied under the six sets of conditions.

In order to simplify the expression of the results and to give a numerical value to the concentration of the irritant on the one hand and to the intensity of the response on the other we used the arbitrarily defined Index of Irritation described in the former experiment. Table 6 records these values for the six conditions observed in this experiment.

This experiment permits paired comparisons to be made of patch tests with graded concentrations of Tr. cantharides under the following conditions. The Sign test for statistical significance was applied in each instance.

1. *Tr. Cantharides Alone and with an Immediate Mild Erythema Dose of U.V.L. (Columns A and B in Table B2).*—While the recorded Indices showed a higher reaction in 7 of 9 persons (2 were tied) when the two irritants were administered these results were not statistically significant, and our impression was that the variations of reactions were within the limits of chance, considering the numerous variables intrinsic in this type of experiment. It might be speculated that there would be a summation of two primary irritants of different sorts, i.e., U.V.L. and Tr. cantharides when nearly simultaneously administered or their effects might have canceled out to some extent.

2. *Irradiated Without Stripping (D) Vs. Unirradiated Without Stripping (F).*—The Indices of reactions on the irradiated area as compared with the unirradiated control arm when no stripping was done would indicate that there might be a slight protective effect against Tr. cantharides from the ultraviolet exposures, although the Sign test indicated no statistical significance.

3. *Irradiated Without Stripping (D); Unirradiated With Stripping (E).*—Comparing the results on irradiated areas without stripping with those on the stripped skin without irradiation gave the maximum differences. This might be interpreted to mean that the irradiation decreased the reactivity and the stripping increased the reactivity from normal. The Sign test applied to this comparison indicated 5% significance and 3% by the Rank test.

4. *Irradiated Without Stripping (D); Irradiated With Stripping (C).*—Comparing the results of stripping against no stripping on irradiated skin indicated a slight difference which was statistically insignificant by Sign and Rank tests, but the difference was in the direction of stripping

increasing the irritability of the skin to Tr. cantharides.

5. *Irradiated with Stripping (C); Unirradiated with Stripping (E).*—Comparing the results of the irradiated against unirradiated areas when both were stripped would indicate that there was somewhat less reaction with irradiation than without, but Sign and Rank tests were insignificant.

6. *Irradiated With Stripping (C); Unirradiated Without Stripping (F).*—When the stripped irradiated areas are compared with the unstripped unirradiated areas no difference could be seen.

7. *Unirradiated With Stripping (E); Unirradiated Without Stripping (F).*—On the unirradiated skin the comparison between the stripped and unstripped skin seemed to indicate a difference with enhanced irritability after stripping, although here again the Sign and Rank tests indicated statistical significance of greater than a 10% likelihood of the difference being due to chance. In spite of the smallness of the series and the lack of statistical significance except in the third comparison above, we believe that the results do permit some impressions. These impressions are subject to several interpretations, the most obvious being that the effect of ultraviolet light increasing the thickness of the stratum corneum may have some protective effect against the irritation of a substance such as Tr. cantharides. Conversely, the stripping of 10 layers of stratum corneum by Scotch tape increased the irritability or reactivity of the skin to the primary irritant in question. This might simply be due to the change in thickness of the stratum corneum although it does not exclude the influence of the electrolytic barrier zone or other cellular, vascular, or humoral elements that enter into the inflammatory reaction.

Controls in this experiment were largely inherent in the paired nature of the comparisons. The solvent for Tr. cantharides was applied as the 0% patch test and biopsy specimens were performed to confirm the expected changes in the skin due to ultraviolet irradiation, stripping, and the type of eczematous reaction expected by patch testing with Tr. cantharides.

Summary

The complexity of the subject of primary irritation of the skin has been emphasized and it is suggested that while many agents may be included as primary irritants the term Primary Irritation usually implies an eczematous response in the skin. Observations on the skin reactions in a group of guinea pigs to threshold concentrations of two primary irritants indicated that the presence of a massive dermatitis may increase the irritability of the skin elsewhere. Observations on the reactions of the skin of a small group of humans indicated that the thickness and integrity of the stratum corneum may have considerable influence on the reactions of the skin to threshold concentrations of a primary irritant.

Adolph Rostenberg Jr., M.D., offered his advice and valued suggestions, Herbert Batson, Ph.D. made suggestions concerning the statistical treatment of the data, and Miss Judith A. Fox gave her technical assistance.

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ABSTRACT OF DISCUSSION

DR. RUDOLF L. BAER, New York: I enjoyed Dr. Haeberlin's paper very much. In the past few decades, a great deal of work has been done on allergic cutaneous reactions. While much remains to be learned, considerable advances have been made in our understanding of these reactions. It is surprising that, during this same era, very little work indeed has been published about the primary irritant reaction, even though this is the much more basic cutaneous response.

Dermatologists for many years have recognized that when substantial skin areas become irritated, patients often present a state of nonspecific increased irritability in the affected, as well as the unaffected skin areas, which must be sharply differentiated from multiple allergic sensitivities (*J.A.M.A.* 170:1041, 1959). Dr. Haeberlin has been able deliberately to produce the same phenomenon in guinea pigs under standardized conditions. He has demonstrated a definite increase in susceptibility to primary irritation in grossly normal-appearing skin areas in these animals at the height of widespread and intense cutaneous irritation elsewhere. This increase in irritability was observed uniformly in all the guinea pigs tested.

He has been conservative in interpreting the results in the second series of tests which were carried out three to five weeks after a major irritation had been produced by painting one entire side of the animal's back with 40% croton oil. It would seem that the weaker responses to croton oil on the side which previously had been irritated with croton oil than on the nonirritated side, in the absence of any differences between the reactions to chrysarobin on the two sides, in itself may well be an important finding rather than a freak occurrence. Perhaps the greater reactivity at the control side only to croton oil and not to chrysarobin was conditioned by the fact that croton oil had been used to produce the major irritation. Therefore, we may be dealing here with a specific change in reactivity, other than an antigen-antibody reaction, produced by a primary irritant.

In all experiments utilizing the method of paired comparison, one must be aware of the hitherto largely unexplained effects, which compounds topically applied to one side may exert on the lesions on the other side. Among these are what Siemens (*Hautarzt* 2:439, 1951) described as a "hitherto undescribed phenomenon of improvement in distant untreated sites in patients treated with hydrocortisone ointment," cited by Sulzberger, Witten, and Smith (*J.A.M.A.* 151:468, 1953).

Another possible source of error, incidentally, is the difference in irritability of different parts of the guinea pig's back. The areas near the neck usually are considerably more susceptible to irritation than the other areas of the guinea pig's back.

Time permits me to make only a few comments about the studies with tincture of cantharides, ultraviolet radiation, and tape stripping in man, where Dr. Haeberlin compared six sets of conditions. He has shown that often-repeated ultraviolet irradiation somewhat increases the skin's resistance to the irritant effects of tincture of cantharides and suggests the phenomenon of thickening of the horny layer, originally described by Miescher, as a reasonable explanation. In addition, one might consider other physiologic effects which are brought about by the daily production of an ultraviolet erythema at the test sites. For example, there may well be a relative deficiency or an exhaustion of certain tissue constituents which are helpful or essential for the occurrence of irritant reactions due to tincture of cantharides. Dr. Haeberlin's other finding is not unexpected. If one deprives the skin of its protective horny layer, one increases the irritation engendered by tincture of cantharides.

If one considers spongiosis and intra- and intercellular edema as the cardinal expressions of eczema in histologic sections, then tincture of cantharides cannot be called an eczematogenic agent. Histologic studies presented by us before this society two years ago showed that tincture of cantharides primarily produces a parenchymatous damage which is very different in its evolution and appearance from a true eczematous reaction (Baer, Rosenthal, and Sims: A.M.A. ARCH. DERMAT. 76: 549, 1957).

Dr. Haeberlin has presented us with interesting new data on primary irritation, a much neglected subject, despite its practical and theoretical importance.

DR. MAURICE SULLIVAN, Baltimore: I was pleased that Dr. Haeberlin chose the subject of primary irritation for his initial presentation before the Association. Whereas there has been a tremendous amount of work reported on cutaneous hypersensitivity, the subject of primary irritation has not received comparable attention. This is understandable when it is realized how difficult it is to perfect accurate threshold for primary irritants. There is some confusion regarding testing procedures for primary irritants. This is due in part to a misunderstanding about the manner in which tests for primary irritation should be applied. Dilutions of primary irritants have been used to test for primary irritation. It is not appropriate, in my opinion, to dilute primary irritants when testing for primary irritation. If a primary irritant is diluted you may change the surface tension, the viscosity, the pH and depending on the diluent, you may change the absorbability. The buffering action of the diluent also changes the reactivity pattern. For the determination of graded reactions, ac-

curately measured, undiluted small amounts should be applied until an amount is reached where there is no discernible reaction. This is very difficult but not impossible to achieve if micropipette techniques are employed.

I enjoyed Dr. Haeberlin's presentation very much, but I believe his results would have been more convincing had he employed testing procedures with undiluted substances.

DR. A. ROSTENBERG JR., Chicago: I think that Dr. Haeberlin's interesting experiments have added to our knowledge of what we might call the homeostatic function of the skin, and I think it is well that we emphasize more the paramount importance of the skin in maintaining our equilibrium, indeed, our very survival.

Dr. Haeberlin has been very cautious in drawing conclusions from his results, and, correctly so, but I, not being the author, can speculate with greater freedom as to possible interpretations. I think the one interpretation he did bring out is one that is of considerable practical importance; namely, the nonspecific over-all heightened irritability of the skin at the time of a massive cutaneous insult.

I should guess that this insult does not have to be an irritation based solely on a primary irritation, but on allergic eczematous reactions as well. This becomes of practical importance, for example, in testing new compounds or endeavoring to make predictions concerning the primary irritant potentialities of new compounds. Von Haam and Emmerich have shown that if you take an inbred population, that is, a group of "volunteers," whom you use, for test purposes, over a long period of time, you will find that, after a while, the reactivity of their skin becomes abnormal. They are no longer suitable subjects for evaluation of new compounds, so I think it behooves those of us here who do this type of work—and this is important work for industry—to remember that it is very handy to have an inbred population, but, sooner or later, you are probably going to come out with a wrong answer, because of this.

I had the privilege of reading Dr. Haeberlin's paper as it will be published, and, of course in the paper he goes at length into the possibility that under the label "primary irritation" there may not be a homogeneous set of reactions. Some of the discussers have hinted at this. This might explain some of the differences he saw, say, between croton oil and chrysarobin. It may be that the healing time with these two is quite different, even though, ostensibly, the guinea pigs look entirely healed, actually, the effects of the two might linger on in a different way, so that the retesting phenomenon was different, as he found out.

Finally, I think some of these studies do explain the term—I think originally created by Bloch—of polyvalent sensitivity. This has always been a somewhat mysterious expression and, to me, it did not have too much meaning. Of course, by polyvalence to sensitivity we have to distinguish between true multiple sensitizations and polyvalence, denoting an enhanced capacity for reactivity. I think often this enhanced capacity arises for the reasons Dr. Haeberlin gave and not because of the acquisition of new allergic sensitivities. We all know that a person can be violently sensitive to poison ivy, and yet go through life with only this one highly specific sensitivity.

DR. JOHN B. HAEBERLIN JR. Chicago (closing): In the written paper we go into the question of the magnitude of the scope of primary irritation as Dr. Rostenberg suggests. Of course, considerable work was done in preliminary studies to select irritants which would produce a graded response to graded concentrations and chrysarobin and croton oil were used on guinea pigs for this reason. However, when we tried to use these same irritants on humans, we could not find graded dilutions that would give satisfactory gradations of reactions. On human skin tincture of cantharides gave much more consistent and graded reactions in our experience.

Recurrent Cushing's Syndrome with Trichophyton Rubrum Infection

LAWRENCE M. NELSON, M.D., and KENNETH J. McNIECE, M.D., Santa Barbara, Calif.

The effects of adrenal hypercorticism on bacterial infections are well recognized. The effects of hypercorticism on mycotic infections are not as widely appreciated. The following case warrants reporting because the patient shows dramatically the effect of hyperadrenocorticism on a Trichophyton rubrum infection. The steroid assays on this patient with adrenal hyperplasia and adenomas were within the levels usually found in adrenal malignancy.

Report of a Case

A white married engineer, aged 30, was seen at the Clinic in June, 1954, because of progressive weakness of six months' duration, obesity, known hypertension, and a dermatitis which had first appeared in September of 1953. Pertinent physical findings at that time were moderate obesity (height 72 in., weight 220 lb.), a blood pressure of 200/140 (which dropped rapidly to 140/100 on bed rest and reserpine), and electrocardiographic evidence of early left ventricular hypertrophy. Erythematous, scaling plaques, more active at the borders, were seen on the arms, forearms, dorsum of the right hand, and on the legs, groin, and feet. Follicular pustules were present on the legs. All the toenails and all except the right and left third fingernails were thickened and friable. Mycelia were demonstrated in scrapings from the skin and from the nails. Trichophyton rubrum grew on culture. Aside from a diabetic type of glucose tolerance curve, laboratory work at that time was noncontributory. The patient was placed on a high-protein reducing diet, reserpine for his hypertension, and diamthazole dihydrochloride (Asterol) ointment for the mycotic infection.

Despite a 20-pound weight loss, reexamination in September, 1954, showed the face to be "moon-shaped," and he had developed a definite "buffalo hump." There was blotchy redness of the face and neck, and purple striae were present over the hips and thighs. The mycotic infection had become more extensive. The hair of the left scalp above the ear was thin, and broken hairs appeared as black dots. T. rubrum was cultured from

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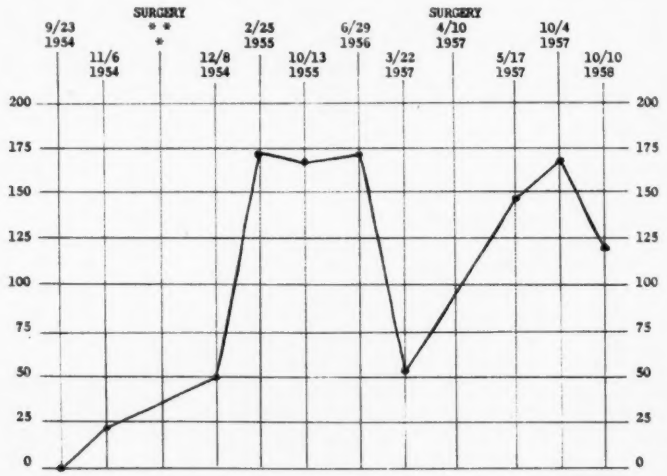

Fig. 1.—Total fasting eosinophil count.

these broken hairs. Impotence had developed since the previous visit, as had pain in the back. X-ray examination of the back showed marked osteoporosis and collapsed vertebrae. A fasting eosinophil count was zero. The 17-ketosteroid excretion reached a maximum of 78.3 mg/24 hours, and 17-ketogenic steroid excretion reached a maximum of 127.5 mg/24 hours (normal: 9-22 for each). The pituitary gland was subjected to irradiation without any improvement in the patient's condition.

On Nov. 24, 1954, the entire right adrenal gland and 90% of the left adrenal gland were removed. The right adrenal gland weighed 16 gm., and tissue removed from the left adrenal gland weighed 6 gm. (normal weight of adrenals: 7-12 gm.). The microscopic diagnosis was "bilateral hyperplasia and hypertrophy of the adrenal cortex and corticoadrenal adenomas." Despite replacement therapy, the patient developed a marked depressive reaction with suicidal tendencies; his postoperative course was otherwise uneventful. The abnormal laboratory findings returned rapidly to normal, and the depression abated. He was placed on a maintenance dose of cortisone, which he discontinued in June of 1955. In February of 1956, the patient was seen for follow-up. At this time there was marked change in his physical appearance. Muscle strength had improved, libido had returned, his blood pressure was 120/82. X-ray examination of the back showed no change in the degree of osteoporosis or in the old fractures. Aside from some thinning of the hair in the area previously involved by the black-dot fungus, the scalp was normal. Some thickening of the distal palms and of the flexors of the fingers was still present. The nail plates were growing out smoothly. When seen in June of 1956, only the right fourth and fifth fingernails showed involvement.

In March, 1957, the patient again complained of loss of strength, weight gain, and a spread of the mycotic infection. Examination showed a return of the moon facies, plethora of the face and neck, and recurrence of the "buffalo hump." The striae were again purple. His blood pressure was 162/82. The T. rubrum infection had spread to involve again several toenails and fingernails, the flexor surfaces of the hands, and the distal soles. The right ear lobe was scaling and erythematous, and the adjacent cheek was erythematous and papular. The glucose tolerance curve was again of the diabetic type. The 17-ketosteroid and 17-ketogenic steroid determinations were elevated. The remaining portion of the left adrenal gland, weighing 9.3 gm., was removed on April 10, 1957. The patient made an uneventful postoperative recovery, without the depression that followed his previous surgery. During the convalescent period, before discharge from the hospital, the facial contours started to lose their puffiness, and his mycotic infection began to subside. The patient was placed on total substitution therapy, consisting of 50 mg. of cortisone daily. The blood pressure rapidly returned to normal, as did the abnormal laboratory findings. The T. rubrum infection continued to improve. In October, 1958, there was involvement only of the right second and fourth fingernails and of the left first toenail. There was slight scaling of the palms and of the heels.

Comment

Burns [2] reviewed the effects of excessive adrenal steroid hormone on experimental animals with fungus infections. In general, experimental fungus infections are spread by the administration of systemic steroids. Not all workers were able to confirm the deleterious effect of steroids on fungus infections. Scheer [17] found that in massive Candida albicans infections, cortisone reduced the severity of the infection in male mice, but not in female mice. Jadassohn et

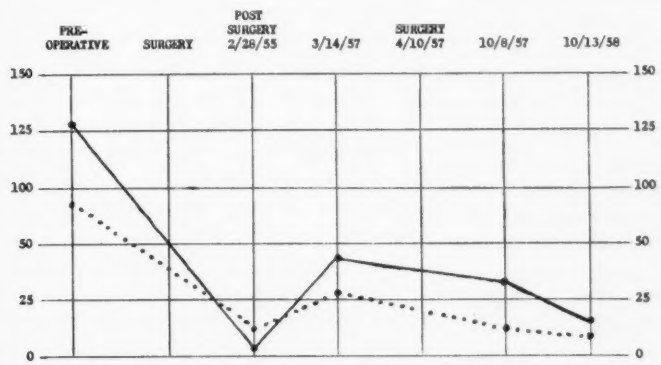

Fig. 2.—Urinary excretion, showing 24-hour excretion in milligrams. Solid line indicates 17-ketogenic steroids; dotted line, 17-ketosteroids.

al.[7] noted no difference between the cortisone-treated guinea pigs and the controls in either the incubation time, the evolution of the first infection, or of the reinfection. Achorion quinckeanum (Trichophyton mentogrophytes) was used. Reiss and Caroline,[15] also using Achorion quinckeanum, found that cortisone did not shorten the incubation time of primary infections, but that it did cause an increase in the duration of the infection. Corticotropin had no demonstrable effect on the course of the infection. Neither steroid influenced reinfection as compared to the controls.

The amount of corticosteroid given to humans is usually relatively much less than that used in experiments in animals. Many humans receive corticosteroid without in any way influencing their mycotic infections. However, there is clinical evidence that adrenal steroid hormone may, at times, adversely affect mycotic infections in humans. Pillsbury and Jacobson[14] presented before the Philadelphia Dermatological Society a 19-year-old man with Cushing's syndrome of four years' duration and a generalized T. rubrum infection of two years' duration. Bratlund and Holton[1] observed 18 patients who developed moniliasis with prolonged (over seven days) steroid therapy. Of these, 8 received hormone alone, or had received no antibiotic within 10 days prior to the observation of the monilial infection. Cremer[3] reported four patients who developed generalized superficial mycotic infections with adrenal hypercorticism. Two of these patients developed Cushing's syndrome and generalized spread of superficial mycotic infection (one with Trichophytin mentagrophytes, the other Trichophytin tonsurans [crateriform]) while receiving corticotropin for thrombocytopenic purpura. The other two patients who had Cushing's syndrome (one with T. rubrum of the skin and C. albicans of the mouth, and one with T. mentagrophytes of the skin) improved greatly after successful bilateral adrenalectomy without treatment of the mycotic infections. Smith and Cleve[20] observed a case of moniliasis and one of histoplasmosis develop during cortisone therapy. Fergusson[6] cites one patient with reticulosis of the skin whose tumors regressed under corticotropin therapy while a T. rubrum infection spread quickly over the trunk. No signs of overdose are noted, and the period of administration and amount of the steroid are not given. Silverman et al.[19] have noted the spread of histoplasmosis under steroid therapy. Burns[2] observed spread of a Cryptococcus neoformans infection while the patient was given adrenocorticotropin hormone and cortisone.

While corticosteroids may adversely affect infections, properly used they may be of great help in combating infection and its effect. It is well known that proper administration of corticosteroids is necessary to combat infection in patients with Addison's disease and in patients who have undergone surgical adrenalectomy. In overwhelming bacterial infections, the corticosteroids may permit survival of the patient until antibiotic treatment has time to take effect.[8,10] The antibiotic treatment must be continued for some time after the corticosteroid has been discontinued. In these patients the corticosteroids apparently act by depressing the toxic or allergic effect of the bacteria. The same result has been noted on the allergic skin symptoms of primary coccidioidomycosis[5,12] and of kerion.[18]

The mechanism of interference with immune reactions by the corticosteroids is not completely understood. The effect must be mediated via the patient's ordinary defense mechanism, as cortisone has no effect in vitro on growth of microorganisms.[9,13] It likewise failed to influence the bacteriostatic or bactericidal effect of antimicrobial drugs in vitro.[9] Corticosteroids diminish capillary permeability, and, in sufficient dosage, decrease the inflammatory response to a variety of irritants. They also diminish antibody production and alter the reticuloendothelial function. The negative nitrogen balance may also have a part in lowering

resistance to infection.[11] The increased glucose level in the patient here reported may have aided the spread of the mycotic infection, although Rothman[16] found the most recalcitrant T. rubrum infections occurred in patients with relatively flat glucose tolerance curves; he postulated that the fungi were able to adapt themselves to metabolize substances other than glucose.

Those patients who have had mycotic infections adversely affected by adrenal steroids have had either a severe underlying disease for which the steroids were administered, or have had excessive endogenous steroid secretion. Either condition could cause decreased host resistance. It is probably the decreased host resistance, rather than increased virulence of the fungus, which allows for the severe, generalized spread of the infection. It should be noted, however, that an apparent increase in virulence of tinea infections contracted from a patient[15] and from mice[4] with adrenal hypercorticism has been observed.

Summary

A patient with Cushing's syndrome and a Trichophyton rubrum infection is reported. On two occasions, spread of the T. rubrum infection was one of the early symptoms of overactivity of the adrenal cortex. Corticosteroid levels were increased to the levels usually found in adrenal malignancy, although hyperplasia and adenomas were found microscopically. Twice, when steroid levels returned to normal, the Trichophyton rubrum infection promptly subsided to minimal involvement of nails and adjacent skin.

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Cushing's Syndrome and Dermatomycosis

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Introduction

Cushing's syndrome, whether it reflects primary adrenal cortical hyperfunction, or hypercorticalism secondary to pituitary basophilism, is a rare disease. A review of the records at the Bronx Veterans Administration Hospital for the period 1948—1958 produced a total of only eight such cases. During this period the hospital was averaging approximately 9,300 admissions annually, underlining the rarity of this syndrome.

Extensive mycotic cutaneous infection due to Trichophyton rubrum is uncommon in a temperate climate such as that of the northeastern United States. We are referring to the widespread infection rather than the localized variety of dermatomycosis, which may have started as a tinea cruris or tinea pedis and spread to involve the adjoining buttocks or feet. One probably does not see more than one or two new cases a year of a generalized T. rubrum infection in a New York City dermatologic center. The rarity of this condition was also emphasized by Lewis et al.,[9] although, in the discussion that followed, it was pointed out that this might hold true only for the temperate northeast climate.[23] In support of this, colleagues from the southern United States have informed us that extensive dermatomycosis is not uncommon in their areas.

Among the eight cases of Cushing's syndrome were three with an extensive dermatomycosis. We feel that this high incidence of a condition rare to our region, in the course of another even more rare disease, might well be more than fortuitous and merits further discussion.

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Report of Cases

CASE 1.—The patient first developed an eruption on the left palm at the age of 22. He was told at that time that he had a fungus infection, but treatment was unsatisfactory. Within the next two years there was a generalized spread of the fungus infection to the buttocks, thighs, legs, arms, and axillae. During this time the patient was found to have hypertension. At the age of 28, he noted increase in weight, enlargement of the abdomen, and the appearance of bluish streaks on the anterior abdominal wall. He then developed progressive pain in the back and was finally hospitalized at the age of 31.

Physical examination at that time revealed an obese white man with florid facies, bull neck, and a markedly obese abdomen with purplish striae. There was hepatomegaly. Blood pressure was 190/130. There was deformity and splitting of the fingernails. A brownish, scaling, confluent eruption encompassed the legs, thighs, buttocks, hands, arms, and axillae.

Laboratory examinations revealed a 3+ albumen and 3+ sugar in the urine. Fasting blood sugar was 165 mg. %. Sodium, potassium, and chloride serum levels were normal. Circulating eosinophils were low. Urinary 17-ketosteroids and oxysteroids were normal to low. Repeated cultures from various areas of the involved skin revealed T. rubrum. A skeletal survey showed diffuse osteoporosis, several rib fractures, and fractures of the vertebrae L-2 to L-4.

Despite left adrenalectomy and pituitary irradiation, the patient remained hypertensive, had several episodes of cardiac decompensation, and finally died.

CASE 2.—The patient noted a rounding of the face at the age of 20. The following year, on routine physical examination, he was found to have asymptomatic hypertension as well as a generalized fungus infection. During the next three years he experienced low back pain, increasing in severity until walking became impossible and hospitalization was necessary.

Examination on admission showed a 24-year-old, very short, plethoric white man. Blood pressure 180/130. Purplish abdominal striae were present. The palms and soles were a dull-red color. There was a generalized, dry scaling of the feet, legs, thighs, buttocks, abdomen, back, and arms.

Laboratory examinations showed a 2+ urinary albumen; 24-hour urinary 17-ketosteroids were 17.8 mg. and 11-oxysteroids were 5.6 mg. X-ray examinations showed diffuse osteoporosis with collapse of several vertebrae. Cultures of the skin lesions showed T. rubrum on three occasions from various sites. The patient eventually died despite adrenalectomy.

CASE 3.—This patient gave a history of having diabetes diagnosed at the age of 22. He was told at that time that he had a fungus infection of the feet. At the age of 26 he noted a swelling of the cheeks, chest, and trunk. The following year he developed a compression fracture of D-12 following trauma. In the next two years he developed progressive tiredness and weakness which finally necessitated hospitalization.

Physical examination on admission showed a somewhat plethoric, 29-year-old white man, with full cheeks, chest, and abdomen, and sparse chest hair. Blood pressure was 144/100. There were erythematous, nonelevated, scaling plaques on the right knee, left lower leg, the dorsum of the left foot, and both soles.

Laboratory examinations showed a 4+ urinary sugar and a normal hemogram; 24-hour-urinary 11-oxysteroids were 2.7 mg. preoperatively. The 17-ketosteroids and 11-oxysteroids were normal in several postoperative follow-up examinations. X-rays showed a diffuse osteoporosis, a compression fracture of D-12, and a normal sella turcica. Perirenal air insufflation showed an enlarged left adrenal.

Shortly after admission, there was a rapid spread of the skin lesions to involve the buttocks and trunk. Whereas E. floccosum was first cultured out of the skin scrapings, soon T. rubrum was found on various areas. The pituitary was irradiated, and the enlarged left adrenal removed. Following the operation the cutaneous lesions regressed rapidly, except for several minor flare-ups, leaving the patient with only a persistent tinea pedis and a tinea manuum.

Discussion

The coexistence of Cushing's syndrome and a widespread dermatomycosis has not gone unnoticed. Pillsbury [13] presented such a case before the Philadelphia Dermatological Society. Cremer [2] described two cases of dermatomycosis, one of which was very extensive, in patients with this syndrome.

Attention has also been paid to the problem of fungus disease as a complication of steroid therapy. This creates an analagous situation in that the prolonged therapeutic use of corticosteroids in large doses may produce an iatrogenic Cushing's syndrome.

The influence of corticosteroids on the response of animals inoculated with fungi has been studied experimentally. Most of the animal experimentation has dealt with Candida albicans, Coccidioides immitis, Histoplasma capsulatum, Actinomyces, and Cryptococcus neoformans,[4,10,12,17] pathogens capable of producing systemic disease. There appears to be general agreement that the dissemination of deep fungus infections in the experimental animal is favored by the use of systemic steroids.

Much has also been written on the clinical aspects of serious, systemic fungus infections developing during the course of steroid therapy.[1,18,19,22] Although some authors feel that few patients infected with Coccidioides immitis have suffered a dissemination purely as a result of steroid therapy,[8] others [1,18,19] feel that such therapy may be a factor in the dissemination of deep fungus infections. The consensus is probably that expressed by Burns [1] when he states that prolonged and high-dosage steroid therapy, administered to a patient with serious systemic disease who harbors a focus of mycotic disease, will favor the promotion of serious systemic fungus disease.

When it comes to a discussion of the influence of steroids on the superficial fungus infections, the dermatomycoses, there is much less experimental and clinical material from which one can draw any conclusions. Kligman et al.[7] studied the effect of systemic steroids in superficial fungus infections in animals and found that cortisone delayed the healing time of the guinea pig experimentally inoculated with T. mentagrophytes. Jadassohn et al.[5] performed a similar experimental study but could find

no difference between the cortisone-treated and the control guinea pigs. Reiss et al.[15] found that cortisone could prolong the course of the primary mycotic infection in guinea pigs. He was also able to suppress the trichophytin reaction in eleven out of twelve sensitized rabbits treated with corticotropin (ACTH).[16] The above experimental material possibly points to the corticosteroids producing some decrease of resistance in experimental dermatomycosis.

There have been only few clinical reports concerning the effect of systemic steroids on superficial fungus infections. Cremer[2] reported on two cases of dermatomycosis definitely aggravated by the prolonged use of corticosteroids for a coincidental thrombocytopenic purpura. We have recently seen a patient who has been on corticosteroids since 1951, and who has developed a widespread and extensive tinea versicolor in the last year. This in itself is not uncommon, but the extension may be indicative of an unusual response in a special terrain.

It is possible that the aggravation of a dermatomycosis during corticosteroid therapy is truly uncommon. The dissemination we have noted in the primary Cushing's syndrome may be associated with steroids other than hydrocortisone, whereas it is the latter and its analogues that are ordinarily used therapeutically. Then again, the aggravation of a dermatomycosis may possibly be more common than realized, but the patient may not be brought to the attention of the dermatologist. The plethora, the striae distensae, the acneform eruption and other cutaneous changes of the iatrogenic Cushing's syndrome may tend to mask any widespread dermatomycosis to the inexperienced eye. However, one can only argue these points by analogy because of the paucity of clinical information on the subject.

In contrast to our inability to take any real stand on the relationship of steroid therapy and dissemination of dermatomycosis, we feel that there is a very definite relationship between the latter and the spontaneous Cushing's syndrome due to intrinsic adrenal disease or pituitary basophilism. Our own cases have firmly convinced us that this relationship is not purely a fortuitous coincidence.

The small number of cases involved prevents our findings having any real statistical validity. However, certain clinical considerations favor the opinion that there is a distinct relationship. As mentioned earlier, extensive dermatomycosis is uncommon in the New York City area, yet three out of eight cases of Cushing's syndrome (almost 40%) presented extensive dermatomycosis. Also, the patient in Case 3 showed a definite and rapid clearing of his dermatomycosis, except for a residual tinea pedis and manuum, following successful adrenalectomy and pituitary irradiation. This is similar to what occurred to Cremer's patient with extensive dermatomycosis following adrenalectomy.[2]

It should be pointed out that in all three cases a T. rubrum was cultured from all involved areas. The significance of this escapes us at this time. This may simply reflect the increased incidence of T. rubrum infections. Then again, it may reflect a tendency to increased virulence or more favorable growth conditions for T. rubrum, as compared to the other dermatophytes, when growing on the skin of a patient with Cushing's syndrome.

Mechanism of Spread of Infection

The in vitro effect of various steroid hormones on the culture of pathogenic fungi[14] has been studied to determine whether there is any direct interference with the metabolic processes of the fungus. Any direct stimulating effect of steroid hormones on the dermatophyte might easily explain any tendency to dissemination of dermatomycosis during prolonged steroid therapy and in patients with Cushing's syndrome.

According to Delamater[3] there is no evidence that pathogenic fungi require steroid hormones for growth. Reiss[14] evalu-

ated the effect of 12 different steroid hormones on 14 species of pathogenic fungi. Various species were affected differently by various compounds. In general, the effect was fungistatic in a variable fashion, except for Candida albicans and Torula histolytica, which showed an enhanced growth. Using the same technique, we ran a study with hydrocortisone, which Reiss had not used, to determine the effect on T. rubrum. There was no significant increase in rate of growth or absolute amount of growth as compared to controls. Apparently, any tendency to increased dissemination of dermatomycosis is not due to the direct stimulating effect of the steroid hormone on the dermatophyte.

Since the corticosteroids have no direct effect on dermatophyte metabolism, enhancing its growth, then the possibility must be considered that they exert an indirect effect on fungus growth through the influence of the steroids on the host inoculated with the fungus. The corticosteroids have a definite influence on the spread of bacterial and viral infection through suppression of various immunological defenses, such as depression of lymphoid tissue mass, antibody synthesis, fibroblastic proliferation. All of these represent a depression of the reticuloendothelial system and a decreased immunological response.[6,11,21,22] Dermatomycosis, even though it is a superficial infection, produces immunological reactions.[20] Changes in the host-fungus immunological relationship may be the direct effect of the excess steroids of exogenous (therapeutic) or endogenous (hypercorticalism) origin. The findings based on the bacterial and viral studies may be of possible application to the spread of fungus infection. It may be the changes in the host immunity factor that favor fungus dissemination in the host.

There is a possibility that the high incidence of disseminated dermatomycosis in Cushing's syndrome is not specifically due to an increase in endogenous corticosteroids directly, but is merely the result of a breakdown in immunological defenses of a patient with severe systemic disease. This would be similar to the cases of generalized T. rubrum infection associated with systemic lymphoblastoma, such as the cases reported by Lewis et al.[9] Against this argument is the low incidence of generalized dermatomycosis in other serious systemic diseases, such as the various lymphoblastomas. These are far more common than Cushing's syndrome, yet the incidence of generalized tinea infection in these patients is extremely low.

Conclusions

This association of T. rubrum infection and Cushing's syndrome has a definite clinical importance. Case 1 is that of a young man who for at least four years prior to the onset of the classical Cushing's symptoms had an extensive tinea corporis associated with an unexplained hypertension. Case 2 is also that of a young man with unexplained hypertension and a widespread dermatomycosis, present at least two years prior to development of low back pain. Only after three years of this pain was the patient finally diagnosed as having a Cushing's syndrome. Case 3 had diabetes associated with dermatophytosis for some years, but in his case a disseminated dermatomycosis did not develop until after a clear-cut Cushing's syndrome had appeared.

The first two cases demonstrate the obvious diagnostic value of a generalized dermatomycosis associated with an unexplained hypertension, when occurring in an area where extensive tinea infections are uncommon. In any geographic area where an extensive tinea infection is seen infrequently, one should maintain a high index of suspicion for the possible presence of a severe systemic disease. When, in addition, there is present an unexplained hypertension, or the other common symptoms of Cushing's syndrome, diabetes or backache, then one's attention should definitely be attracted to the pituitary-adrenal axis as the possible source of a severe systemic disease.

Summary

Three cases of widespread and extensive dermatomycosis were observed among eight cases with Cushing's syndrome.

This high incidence of generalized dermatomycosis among patients with Cushing's syndrome, in a geographic region where generalized tinea infections are rare, appears to be more than a fortuitous association.

The dissemination of the fungus infection, due to T. rubrum in all our cases, is probably due to changes in the host immunity factor as a direct result of the effect of the excess corticosteroids on the immunological defenses of the host.

The presence of generalized dermatomycosis in association with unexplained hypertension, diabetes, or backache should make the clinician think of the possibility of Cushing's syndrome.

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ABSTRACT OF DISCUSSION

ON PAPERS OF DR. CANIZARES, DR. SHATIN, DR. KELLERT, AND DR. NELSON, DR. MCNIECE

DR. J. WALTER WILSON, Los Angeles: That fungous infections could become worse, even to the point of fatality, during the administration of large doses of corticosteroids or corticotropin (ACTH) was reported as early as 1950 by Soffer, Levitt, and Baehr (The Use of Cortisone and ACTH in Acute Disseminated Lupus Ery-

thematosus, Arch. Int. Med. 86:558, 1950). Fungal infections of lesser degree have been reported as becoming more severe or extensive during such therapy by more than forty authors. A wide variety of species of pathogenic fungi has been implicated in these studies. Animal experimentation has supported this effect in the systemic mycoses much more convincingly than in the dermatomycoses.

Because I believe that the immunity which is so readily acquired to the deep fungous infections by most normal individuals is closely associated with hyperergy to products of the fungus, and that steroid therapy can interfere with its development, I have accepted the dictum that such treatment should be avoided in the presence of known systemic mycoses, except to ameliorate, mildly and temporarily, severe mycids.

However, I am sure that we should not readily accept a direct cause-and-effect relationship between the exacerbations of fungous diseases and Cushing's syndrome, be it the result of pituitary or adrenocortical disease, or of iatrogenic orgin. The total number of cases included in the literature is surprisingly small when contrasted with the number of persons who have received steroid therapy. I know of only three cases of deep fungous infection occurring during steroid therapy in the Los Angeles County General Hospital among thousands receiving such treatment, several hundred in large dosage and over a long time.

As to the deleterious effect of steroid therapy on dermatomycoses, I am still in doubt as to the causal relationship. When Rothman (Rothman, S.: Systemic Disturbances in Recalcitrant Trichophyton Rubrum Infections, A.M.A. Arch. Dermat. & Syph. 67:239, 1953), in 1953, reported that most of his patients infected by Trichophyton rubrum exhibited glucose tolerance curves lower than normal, I began to test some of my patients similarly. Thus far, I have found none with low curves, but several with high ones. I know of five diabetic persons who are chronically infected with T. rubrum, four of whom believe the fungous infection to have postdated the development of diabetes. I know of two more persons who have chronic T. rubrum infection who exhibit glycosuria when on steroid therapy.

I believe it is significant that Doctor Nelson's case showed diabetic tendencies during the time that the Cushing's disease was uncontrolled, and that these times coincided with the exacerbation of the fungous infection. Two of Doctor Canizares' three cases were also diabetic. The sugar tolerance of the third patient was not stated, if determined.

Whether or not a person is to become diabetic is apparently not influenced by the presence of pituitary or adrenal tumors. Therefore, some cases of Cushing's disease develop diabetes and some do not. The percentage is much less than the 75% at least of the cases reported here today with concomitant T. rubrum infections.

It is also known that certain persons develop diabetes during steroid therapy, at least temporarily. It is now generally accepted that these persons were actually potentially diabetic even before the steroids were begun, and the tendency only thereby rendered manifest.

I do not mean to imply that diabetes explains all of the complicated matter of susceptibility to T. rubrum. The long continued unilaterality of this infection, which is so impressive in some 30% of cases, would in itself deny such a thesis, unless the cells of the epidermis of one hand or one foot can be diabetic without the other being similarly involved, and which, by the way, I am not sufficiently erudite to consider impossible. I believe that the ability to become infected by T. rubrum is possessed by certain individuals inherently, and that it is simply brought into clinical evidence by hypersteroid states.

I also know of several patients who have developed severe, generalized T. rubrum infection while under heavy and long-continued steroid therapy, who do not show any tendency toward developing diabetes.

After working with the new oral antifungal drug, griseofulvin, for eight months, I have concluded that it can perform well even in persons possessing any of several systemic diseases, including diabetes. However, I have also seen no reason to change my belief that T. rubrum infects only persons who are immunologically defective in some hitherto undiscovered manner. Griseofulvin does not change this fundamental susceptibility, and these patients are thus very likely to become reinfected when the drug is stopped.

It must still be said of T. rubrum that we understand the total of its talents rather poorly. The studies presented today add another block to a slowly increasing supply of building materials, which I hope will some day suffice to construct a theory leading to our complete understanding of the complicated mechanisms of this type of infection.

DR. GEORGE M. LEWIS, New York: It is probable that the immunologic aspect of the subject, when fully understood, will unlock the answers to this problem.

However, one should not lose sight of the capacity of this organism to induce unusual dermatologic manifestations and, at times, to be associated with systemic complications. Some 29 years ago John Harris and I published a paper in the ARCHIVES, which, presumably, because of its ancient vintage, is often overlooked (Arch. Dermat. & Syph. 22:1 [July] 1930). This report concerned a man, aged 33, with bandlike granu-

lomas of the neck. Hairs removed from the area revealed hyphae outside the shaft; cultures grew out T. rubrum (purpureum); a biopsy demonstrated granulomatous changes. This, as far as I know, is the first instance of a granulomatous response to this organism reported in the American literature—not that I am counting on "firsts," but I simply mention it to show the length of time that an invasive capacity for this organism has been known.

In 1938, a paper on the cutaneous manifestations of T. rubrum by Montgomery, Hopper, and myself (Arch. Dermat. & Syph. 37:823 [May] 1938) was thought to describe a complete syndrome, mentioning all the clinical features capable of being produced. As we now know, other varieties of cutaneous and granulomatous involvements still had not been recognized.

More recently (A.M.A. Arch. Dermat. & Syph. 67:247 [March] 1953) three instances of association of this organism with lymphoblastoma were reported by Lewis, Hopper, and Scott, one case being a patient of Dr. Maurice Costello's.

It is therefore not too surprising to me that Canizares and Nelson have discovered still another association of diseases involving that ubiquitous dermatophyte, Trichophyton rubrum.

DR. STEPHEN ROTHMAN, Chicago: In reply to Dr. Wilson, I first would like to say that indeed our findings of conspicuously flat glucose tolerance curves on 13 out of 20 patients with Trichophyton rubrum infection (A.M.A. Arch. Dermat. & Syph. 67:239, 1953) could not be confirmed after we extended our investigation to 52 more patients. The recent findings will soon be published. On the other hand, I doubt very much that the high incidence of T. rubrum infections in Cushing's syndrome is due to the diabetic tendency in this condition. If diabetes were a promoting factor we should see many more diabetic patients with T. rubrum infection than we actually do see.

That patients with Cushing's syndrome have great susceptibility to T. rubrum infection is beyond doubt. In our department, by now, we have observed six patients with Cushing's syndrome and widespread T. rubrum infection. The first such case was presented by Dr. A. L. Lorincz before the Atlantic Dermatological Association in Washington, D.C. in 1950. Similarly to Dr. Nelson's case, in this patient the fungus infection practically disappeared after the patient was operated on.

Thus, there can be little doubt that Cushing's syndrome creates favorable conditions for the colonization and proliferation of T. rubrum on human skin. It is another question whether therapeutically induced hypercorticoidism acts in the same way. So far I have not heard of patients with therapeutic hypercorticoidism having acquired T. rubrum infection. In the last three years 50% of our patients with natural Cushing's syndrome have had T. rubrum infection. This is an extremely high percentage. In contrast, the combination of diabetes with T. rubrum infection has been reported only sporadically.

In one of our patients, tinea versicolor had appeared after the development of Cushing's syndrome.

DR. LOUIS H. WINER, Beverly Hills, Calif.: I have recently studied the histologic sections from a patient with generalized T. rubrum. In one area of the section, stained with hematoxylin and eosin, was an intraepidermal abscess in which no fungi could be demonstrated on periodic-acid-Schiff staining. However, in another area where a keratin plug remained in the center of a follicle abscess, mycelial organisms could be demonstrated in the keratin but not in the pus. This is shown on the slides I have projected. In T. rubrum, when the cellular reaction is absent, the organisms grow luxuriantly, and when the infiltrate is present, the organisms are difficult to find.

DR. EARL W. NETHERTON, Cleveland: It is interesting that the clinical course of a superficial infection caused by a certain fungus, T. rubrum, may at times be dramatically influenced by a particular endocrine disturbance, namely, Cushing's syndrome.

A number of years ago I observed a patient with a complex problem which was practically identical with the case reported by Dr. Nelson. I wish to give a brief report in order to add one more case to the small number that have been referred to by Dr. Canizares and Dr. Nelson.

In 1936 a young man came to The Cleveland Clinic with a chief complaint that an abnormal unsightly condition of his finger nails interferred with his occupation as an office worker.

Examination showed that all the finger and toe nails were thickened, friable, and broken. There were numerous round and irregular-shaped, superficial, pink, scaly plaques disseminated over the lower extremities and abdomen. The margins of the plaques were well demarcated. Potassium hydroxide preparations revealed the presence of a fungus in nail material and also in the scales from the erythematous plaques. Cultural studies showed that the fungus was T. rubrum. In addition to the onychomycosis and disseminated dermatomycosis, there were clinical manifestations and endocrine disturbance. There was mooning of the face with permanent flushing, as demonstrated by Dr. Nelson's patient. There were numerous telangiectases on the face and purple striae on the abdomen. There was an abnormal distribution of subcutaneous fat on neck and abdomen. The systolic blood pressure was abnormally high.

Dr. Perry McCullough of the department of endocrinology made a diagnosis of Cushing's syn-

drome in this case. Thorough examination revealed the presence of an adrenocortical tumor. Prior to the removal of this tumor, therapy of the T. rubrum infection was unsuccessful. The patient entered the hospital for removal of the adrenal tumor and he failed to return for further treatment of his fungus infection. The manifestations of Cushing's syndrome regressed nicely following the operation. About two years later he returned for observation. All the nails were normal and the eruption had disappeared. These changes had occurred spontaneously. It was not until a year after the removal of the adrenocortical tumor that the nails had become normal. Over a period of 22 years there has been no return of the onychomycosis. This man returned to The Cleveland Clinic hospital during the past year because of a coronary occlusion. I did not see him at this time, however. Dr. McCullough saw him, and he reported that the nails were normal and there were no cutaneous lesions.

In the case I observed there has been no recurrence of Cushing's syndrome as was the experience in Dr. Nelson's case. Furthermore, the spontaneous disappearance of the associated onychomycosis and dermatomycosis has remained permanent. It is not known why the T. rubrum infection disappeared spontaneously following removal of an adrenal tumor. It is unlikely that this unique response can be explained as an acquired immunity. Metabolic disturbances caused by hormone abnormality of Cushing's syndrome, and possible local tissue or cellular changes which influence the value of the epidermis as a soil for growth of T. rubrum, are factors which may alter the course of this fungus infection in patients with Cushing's syndrome.

Just one more interesting point: in a personal conversation with Dr. Nelson, he mentioned that Cushing's syndrome was seen more often in women; however, his case and all cases of Cushing's syndrome with extensive T. rubrum infection so far reported have been in men.

DR. ORLANDO CANIZARES, New York: We really don't know why this happens, but it seems to be a fact, as has been shown today. Certainly it is gratifying to see our reports supported by other dermatologists.

The possible reaction of the patients with Cushing's syndrome seems to be somewhat different, as Dr. Rothman mentioned, from the Cushing's syndrome caused by the administration of steroids. It is also very gratifying to see that the therapeutic response to this condition to griseofulvin is not affected by the presence of Cushing's syndrome.

DR. LAWRENCE M. NELSON, Santa Barbara, Calif.: Relative to diabetes: The Sansum Medical Clinic, whence this patient was referred, has many diabetic patients. To the best of my knowledge, there has not been a case of generalized rubrum infection occurring in a diabetic. I feel that the spread of the T. rubrum infection is due to a change in immunity secondary to the increased corticosteroid level rather than to the associated increased glucose level. Finland and Kass, as well as Burns, have pointed out the possible mechanism of the interference with the immune reaction by the corticosteroids.

I was certainly glad to have Drs. Netherton and Rothman report additional cases of this syndrome. These reports add additional weight to the belief that the increased corticosteroid level is the precipitating factor in the spread of the T. rubrum infection. I should like to know the sex of Dr. Rothman's patient.

DR. ROTHMAN: Male.

DR. NELSON: Apparently, only males are able to respond in this manner.

Dr. Winer has shown very beautifully, microscopically, that suppuration inhibits the demonstration of mycelial elements in tissue, and, when cellular reaction is absent, as it is when patients receive large doses of corticosteroids, the number of fungi increases and they are easily demonstrated.

Epidermolysis Bullosa Acquisita (Tardive) and Porphyria Cutanea Tarda

An Analytic Comparison of These Two Conditions

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Epidermolysis bullosa is generally considered an inherited process beginning early in life, characterized by bulla formation and by erosions of the skin secondary to minor trauma. Occasionally this symptom complex begins in adulthood with no pertinent familial background. A few of these cases of the so-called tardive or acquired form apparently follow severe drug reactions.[1,2] More commonly, however, the syndrome is found with porphyria cutanea tarda.[3-5] The differentiation of the idiopathic acquired variety and that associated with porphyria may lead to some diagnostic confusion. We have recently had an opportunity to study concurrently a case of idiopathic epidermolysis bullosa acquisita with no associated familial or toxic background, and a patient with porphyria cutanea tarda. It is the purpose of our report to compare these two patients, not only to establish differentiating features, but if possible to shed some light on the mechanism or mechanisms responsible for the epidermolysis bullosa symptom complex.

CASE 1. *Idiopathic Acquired Epidermolysis Bullosa* (EBA).—The patient, a 37-year-old Negro man, was first seen in February, 1957, because of blisters, erosions, and scars over the pressure areas of the extremities and ears. This process apparently began twelve years previously, the lesions always appearing after trauma or prolonged pressure. There has been little flucuation in severity of the reaction, and no relationship to sun exposure has been noted by the patient.

Results of physical examination in February, 1957, were normal except for his skin changes. These consisted of groups of milia associated with superficial scars over the dorsa of his hands, fingers, extensor surfaces of his elbows, lower thighs, knees, and legs, and the lateral and superior parts of his external ears (Fig. 1). The more recently traumatized areas were denuded, erythematous, and somewhat edematous. Blisters up to 10 cm. in diameter were present, chiefly on the anterior thighs, knees, and shins.

In addition, he had dystrophic changes of all the nails, which had been present nine years. These consisted of lifting up and destruction of the nail plate, and degeneration of the nailbed. The palms

Fig. 1 (Case 1).—Showing extensive scarring on the anterior aspects of the lower extremities and milia formation over the knees.

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and soles were uninvolved, and the hair and teeth were normal.

A thorough review of his past and family history revealed no evidence of liver disease, epidermolysis bullosa, porphyria, or other pertinent information.

Routine laboratory examinations, including complete blood counts, urinalysis, sedimentation rates, serologic tests for syphilis, and chest x-rays, were normal. A bromsulfalein liver function test, serum calcium and iodine, total serum proteins, albumin, and globulin determinations, as well as repeated 24-hour urinary porphyrin studies and a stool porphyrin test, were also normal. Repeated potassium hydroxide and cultural examinations of the nails for pathogenic fungi were negative.

Histologic examinations of a blister on the anterior lower thigh, and clinically normal skin from the anterior upper thigh, were interpreted as follows: The tissue from the anterior lower thigh showed mild hyperkeratosis. The epidermis was thin and flattened, with some atrophy of the basal layer due to pressure from a large subepidermal blister which separated the epidermis and dermis throughout the section. There was marked edema in the upper cutis, associated with some fragmentation of the connective tissue. The superficial blood vessels were increased in number, dilated, and many were surrounded by a round-cell infiltrate. Some incontinence of pigment was noted under the bulla, and a large epidermoid cyst was present. A periodic acid-Schiff stain revealed a marked disruption of the basement membrane, which was split, fragmented, and, in many areas, absent. There was some thickening of the superficial blood vessel walls by deposition of periodic acid-Schiff-positive, diastase-resistant material. Elastic tissue stains showed a marked reduction of elastic tissue in the upper dermis and an increase in the lower cutis, suggesting that it had been pushed aside by the edema. No additional information was gained from Van Gieson, reticulum, and thionin stains. The tissue from the anterior upper thigh showed an essentially normal-appearing epidermis. There was mild edema in the upper corium, and a few subepidermal clefts were seen. Mild blood vessel proliferation and incontinence of pigment were noted under the clefts. There was a minimal perivascular round-cell infiltrate in the upper dermis. The superficial blood vessel walls were slightly thickened. Periodic acid-Schiff stains (Figure 3*a* and *b*) showed that the epidermal basement membrane was somewhat indistinct and irregular. The elastic tissue was intact. Van Gieson, thionin, and reticulum stains gave no additional information.

Previously, multivitamin, antibiotic, and antimalarial therapy had proved to be of no value. On Nov. 17, 1958, he was started on a 36-day course of oral edathamil (Calcium Disodium Versenate), 3 gm. a day. No toxic signs or symptoms were noted, and routine blood and urine examinations remained normal. The results of this therapy, as well as urinary porphyrin and zinc examinations, will be compared with Case 2.

CASE 2. *Porphyria Cutanea Tarda (PCT).*—The patient, a 37-year-old white man, was first seen in January, 1958, because of blisters, erosions, and scarring of the face, neck, and hands. The process started three years ago with repeated abrasion and slow healing in the chronically sun-exposed skin. A year later spontaneous and post-traumatic blisters appeared over the dorsa of the hands and fingers. Though there have been fluctuations in severity, the process has persisted to the present.

Results of a physical examination in January, 1958, were essentially normal, except for the skin changes. His general coloring was as follows: dark red hair, brown eyes, and freckled skin. A subtle reddish-brown hue was suffused over the face and neck. He was diffusely tan over the trunk and upper extermities from sun exposure several months previously. Atrophic depigmented areas over the face, neck, and dorsa of the hands and wrists gave a somewhat mottled appearance to these areas. Three blisters, 0.5 to 2 cm. in diameter, were present on the dorsa of the hands, and a few erosions were seen (Figure 2). There was some suggestion of sclerodermoid changes on superficial inspection, but no sclerosis was found on closer examination. No milia were seen at the time, although a small number have developed on his hands subsequently. The palms, soles, and areas not chronically exposed to the sun were uninvolved. The nails, hair, and teeth were normal.

The past history revealed no evidence of liver disease or excessive alcohol intake. He has never had any difficulty with the sun, despite extensive exposures in the South Pacific as well as in the United States, and he has always tanned well. There was no relationship between drug intake and the onset or exacerbations of the skin eruption. The family history was also noncontributory. Urine uroporphyrin determinations were normal in the father, mother, and the patient's two children.

Routine laboratory examinations, including complete blood counts, urinalysis, sedimentation rates, serologic tests for syphilis, and chest x-rays were within normal limits. Blood and urine calcium, serum total protein, serum albumin and globulin, radioactive iodine uptake, icteric indices, and cephalin flocculation studies were all normal. A sulfobromophthalein liver function test in October, 1957, showed 4.3% retention at 40 minutes. Subsequent B.S.P. examinations in February, 1958, and January, 1959, revealed 7.5% and 6.3% retention at 40 minutes. Repeated 24-hour urinary porphyrin studies revealed marked elevations in the uroporphyrins, and to a lesser extent coproprophyrins. No porphobilinogen was seen at any time.

Fig. 2 (Case 2).—Scars and crusted denuded areas are seen on the dorsa of the hand and fingers, and small blisters on the index finger proximally, and on the dorsa of the hand (blisters indicated by arrows).

Histologic examinations of a blister on the lateral aspect of the left midfinger, and clinically normal skin from the dorsum of the left forearm, were interpreted as follows: The tissue from the left midfinger showed a moderate hyperkeratosis. The epidermis was disrupted by a bulla, apparently subepidermal in origin, which extended laterally intraepidermally. The Malpighian cells of the roof, floor, and periphery of the blister showed evidence of degeneration. The bulla contained a few clumps of degenerating leukocytes. The basal layer was generally indistinct. There were moderate edema and some diffuse homogenization of the collagen in the upper one-half of the corium. The walls of the small dermal vessels were markedly homogenous, periodic acid-Schiff-positive, diastase-resistant material. Periodic acid-Schiff-positive, nondiastase-resistant material was present in the prickle-cell layer, except in grossly degenerated areas. The basement membrane was intact, except under the central two-thirds of the bulla. An elastic tissue stain showed a moderate decrease in elastic fibers, especially in the upper dermis. A Van Gieson stain gave no additional information.

The tissue from the left forearm showed hyperkeratosis and a moderate amount of pigment in the epidermis, which otherwise appeared normal. The dermis showed mild edema and minimal homogenization of the collagen. Periodic-acid-Schiff stains showed an intact basement membrane, except at the edge of the section, where there was a separation of the dermis and epidermis. This may have been an artifact. The walls of the small blood vessels of the dermis were markedly thickened due to the deposition of bright-staining, homogenous, periodic-acid-Schiff-positive, diastase-resistant material (Fig. 3-*c* and *d*). The elastic tissue was intact.

He was started on oral edathamil calcium-disodium, 3 gm. a day, on Nov. 10, 1958. This was continued for 28 days. The results of this treatment, as well as the urinary porphyrin and zinc examinations, will be compared with the findings in Case 1.

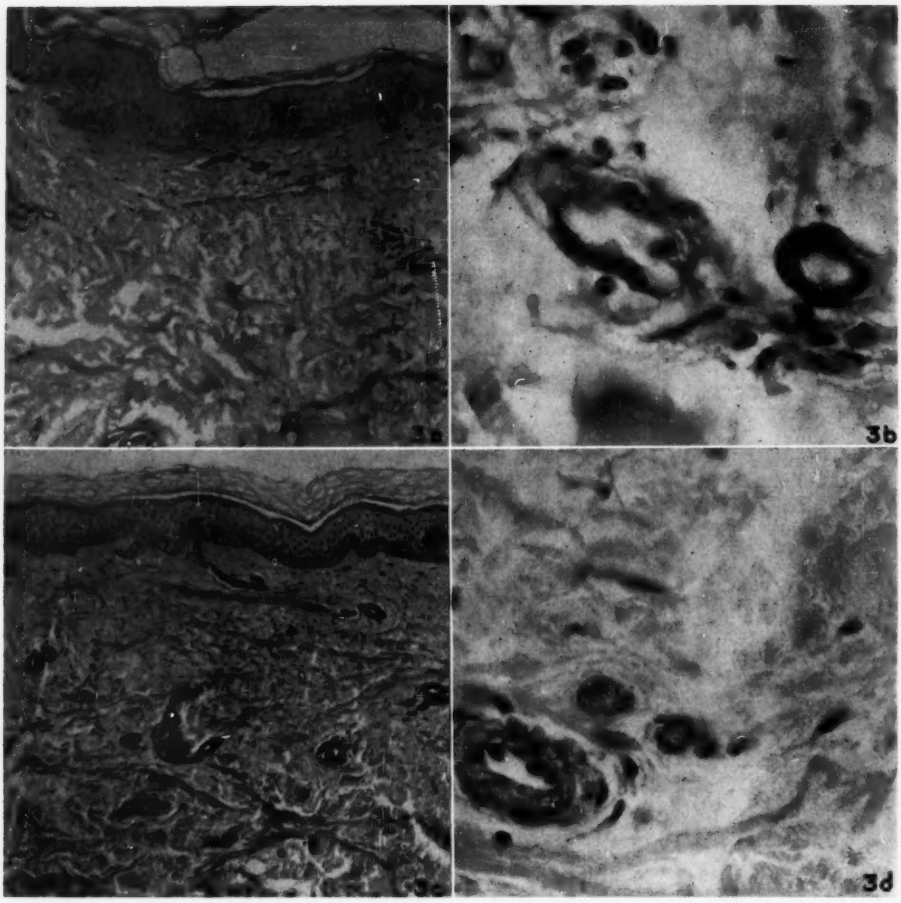

Fig. 3.—Periodic-acid-schiff-stained, diastase-treated sections. (*a*) Indistinct epidermal basement membrane in clinically normal skin, Case 1. × 450 (*b*) Blood vessels in the upper ⅓ of the dermis of clinically normal skin, Case 1. × 900 (*c*) Intact epidermal basement membrane and thickened blood vessel walls in clinically normal skin, Case 2. × 450 (*d*) Thickened blood vessel walls in the upper ⅓ of the dermis of clinically normal skin, Case 2. × 900

*Porphyrin and Zinc Excretion Studies.**—A. Twenty-four-hour urine specimens were tested for coproporphyrin content, using the method described by Strait, et al.[6] After this had been accomplished, the uroporphyrin was extracted with ethyl acetate, and determined by the usual procedures. Porphobilinogen was tested by the Watson and Schwartz method.[7] These examinations were done on five occasions between March, 1957, and September, 1958, on Case 1 (EBA), and six times between January, 1958, and December, 1958, in Case 2 (PCT). Stool protoporphyrin and coproporphyrin were studied in Case 1 (EBA) on March 12, 1959, using the method described by Talman, Holti, and others.[8,9]

The patient with idiopathic acquired epidermolysis bullosa showed no abnormal porphyrinuria at any time, and the fecal levels were within normal limits. The porphyrin excretion in Case 2 with porphyria cutanea tarda was high on all examinations. The levels ranged between 2,720 and 4,850μg. per 24 hours of uroporphyrin, and 350 and 1,010μg. per 24 hours for coproporphyrin. Zinc porphyrin complexes were present. At the end of 28 days of oral edathamil calcium-disodium therapy

* These studies were carried out by Michael Hrenoff in the Spectrographic Laboratory of the University of California, San Francisco Medical Center, under the direction of Louis A. Strait, Professor of Biophysics.

(3 gm. a day) the determinations on Case 2 showed 3,900μg. per 24 hours of uroporphyrin, and 650μg. per 24 hours of coproporphyrin. Porphobilinogen was absent in both cases.

B. The 24-hour urinary zinc excretion was determined, using the method described by Vallee.[10] This test was done on two occasions prior to, and once at the termination of, the edathamil calcium-disodium therapy in Case 1 (EBA), and three times before, as well as at the end of, the treatment period in Case 2 (PCT). The normal values by this method are 457μg., plus or minus 120μg. per 24 hours.

In Case 1, the urinary zinc prior to therapy was 1,410μg. per 24 hours on Sept. 17, 1958, and 1,420μg. per 24 hours on Nov. 12, 1958. After 26 days of the oral edathamil therapy (3 gm. per day) the zinc level rose to 4,190μg. per 24 hours. The values in Case 2 prior to therapy were 374μg. per 24 hours on May 21, 1958; 615μg. per 24 hours on Oct. 8, 1958, and 525μg. per 24 hours on Oct. 22, 1958. The level rose to 3,360μg. per 24 hours after 28 days of taking the chelating agent.

Summary.—As would be expected, the porphyrin excretion was normal in Case 1 (EBA), and markedly elevated in Case 2 (PCT). Porphobilinogen was absent in each. Treatment with the chelating agent had no detectable effect on the porphyrin output in Case 2.

Urinary zinc excretion was normal in the patient with porphyria cutanea tarda, but was definitely elevated in the patient with idiopathic acquired epidermolysis bullosa. The zinc levels increased markedly in both cases after taking edathamil calcium-disodium, indicating that chelation had been accomplished by the oral medication.

Clinical Response to Edathamil Calcium-Disodium Therapy.—The patient with idiopathic acquired epidermolysis bullosa (Case 1) felt that some of his lesions were healing faster, and that his posttraumatic bullae were smaller, after the first two weeks of treatment. However, by the end of 36 days he could see no difference from his pretreatment status. There was no objective improvement at any time. The patient with porphyria cutanea tarda (Case 2) thought that his lesions had begun to heal faster by the end of two weeks of therapy, and, by 20 days, he felt that blister formation, the size of the blisters, and the healing time, had definitely been reduced. Objective comparsion supported the patient's subjective findings. The improvement has lasted three months after cessation of therapy. However, because of the cyclic nature of the disease, the role of the chelation therapy in this response could not be definitely established.

Light Sensitivity Studies.—Tests were carried out to determine the effect of different parts of the electromagnetic spectrum on the skin of our two patients.

The light sources included (1) a Hanovia air-cooled hot quartz contact lamp which emits high energy bands in the erythrogenic range (2,500 A. to 3,300 A.) and the longer ultraviolet spectrum (chiefly at 3,600 A.); (2) a 20-watt standard white fluorescent tube which has a continuous emission throughout the visible spectrum (4,000 A. to 7,700 A.); (3) a 20-watt fluorescent black light which produces a continuous spectrum between 3,200 and 4,100 A. with a peak at about 3,500 A.; (4) 100-watt and 150-watt standard white incandescent tungsten filament bulbs which emit rays in the visible and infrared regions (4,000 to 50,000 A.); and (5) a carbon arc, utilizing National "C" carbons, which produces high energy in the ultraviolet spectrum, 2,200 A. to 4,000 A., with an especially high peak around 3,800 A.

The following filters were used to delineate different parts of the electromagnetic spectrum: (1) window glass to exclude the erythrogenic rays from the hot quartz and carbon arc sources; (2) a 3,391 Corning glass filter to exclude rays shorter than 4,100 A.; and (3) a 5,840 Corning glass filter to exclude all rays except those between 3,000 and 4,000 A. The last two were used only with the carbon arc source.

Test sites were outlined on the flexure surfaces of the forearms and arms, the back, and the dorsa of the hands in each patient. Intense and repeated exposures to wave lengths between 2,500 A. and 50,000 A. were applied to these sites, utilizing the sources and filters described.

The following results were noted: (*a*) No erythema was produced on the dorsa of the hands in either patient, despite prolonged exposure to the erythrogenic rays (2,500 A. to 3,300 A.). This lack of response was probably due to the thick keratin layers and pigmentation of these areas, because of chronic sun exposure. (*b*) No abnormal reaction occurred at any test site.

Summary.—No abnormal reaction was produced in either patient by intense radiation to wave lengths between 2,500 A. and 50,000 A.

Histamine Tests.—Studies were carried out to determine the functional response of the dermal blood vessels to histamine.

Test 1: Histamine diphosphate, 0.05 cc. of a 1:10,000 solution in isotonic sodium chloride, was injected intradermally into the flexure aspect of the right forearm of each case. This was done before and after the edathamil calcium-disodium therapy. The sites were observed for 30 minutes after the injections.

Table 1 demonstrates the results of this study. Case 1 (EBA) developed a normal histamine wheal and flare response. This was slightly more marked after the course of oral edathamil. In Case 2 (PCT), the wheal formation was apparently normal, but the flare response was in-

TABLE 1.—*Histamine Response* *

Case 1	Before Edathamil		After Edathamil	
Time, Min.	Wheal †	Flare ‡	Wheal	Flare
10	12	20 to 30	14	15 to 45
20	13	20 to 25	15	15 to 50
30	14	25 to 30	17	20 to 50
Case 2				
Time, Min.	Wheal	Flare	Wheal	Flare
10	12	2	13	2 to 6
20	12	2	14	2 to 8
30	13	5 (faint)	15	2 to 10

* 0.05 cc. of histamine diphosphate 1:10,000 solution.
† Average diameter in millimeters.
‡ Range of radius of flare from edge of wheal in millimeters.

hibited. The flare reactions as in Case 1 were slightly more marked after chelation. The differences before and after treatment were probably not significant.

Test 2, Case 2 (PCT): One-tenth cubic centimeter of the histamine solution was injected intradermally into the extensor aspect of the left forearm, the flexure area of the right forearm, and the extensor skin of the left thigh. The sites were observed for 30 minutes after the injections. The test was done 85 days after the cessation of the edathamil therapy.

Table 2 shows a marked inhibition of the intensity of the flare response in the extensor skin of the forearm. In addition the reaction in the flexor area of the forearm was greatly reduced in size and intensity, as compared to the response of skin of the thigh.

Summary.—The vascular responses in Case 1 (EBA) were normal. In contrast, the histamine flare reactions were inhibited in the chronically sun-exposed skin of Case 2 (PCT). This inhibition was most marked on the tanned skin of the extensor aspect of the forearm.

TABLE 2.—*Histamine Response* *

Time, Min.	Forearm Dorsa		Forearm Flexure		Thigh Dorsa	
	Wheal †	Flare ‡	Wheal	Flare §	Wheal	Flare
10	15.5	?	18.0	10 to 20	17	20 to 25
25	17.5	?	16.0	9 to 19	18	35 to 39
34	16.0	?	19.5	11 to 15	20	28 to 35

* 0.1 cc. of 1:10,000 histamine diphosphate solution.
† Average wheal diameter in millimeters.
‡ The flare was so faint that it was impossible to determine the borders.
§ Range of radius of flare from the edge of the wheal in millimeters.

Skin Fragility Tests.—Studies were carried out to compare the fragility of the skin of these two cases.

The skin on the dorsa of the hands of each patient was repeatedly stroked with the edge of a tongue blade using heavy pressure. The trauma was confined to areas 1 cm. long and 0.5 cm. wide. The results of this study were as follows: An average of 96 strokes was necessary to denude the skin of the dorsum of the right hand in Case 1 (EBA), whereas an average of only 16 rubs was needed in Case 2 (PCT). No blisters were produced in either patient, even with subdenudation injury. When the tests were repeated after the chelation therapy, the skin in Case 1 was apparently more fragile (44 to 68 strokes were needed). No change was noted in Case 2.

Comment

Differentiation between idiopathic acquired epidermolysis bullosa (EBA) and porphyria cutanea tarda (PCT) at times presents a difficult diagnostic problem. This is especially true since urinary porphyrins are not always elevated in porphyria, and fecal studies are frequently not available.[9] In Table 3 we have listed the clinical findings in each of these diseases.

A comparison of our two cases clearly demonstrates many of the most important differentiating features. The lesions in the patient with idiopathic acquired epidermolysis bullosa occurred on areas most frequently exposed to injury, excluding the palms and soles, and always followed trauma or prolonged pressure. Superficial scarring, milia formation, and dystrophic nail changes were prominent. The uninvolved skin appeared normal. In the patient with porphyria cutanea tarda, the blisters were confined to the dorsa of the hands and fingers, and appeared spontaneously as well as post-traumatically. There was a reddish-brown hue to the skin of the face and neck. Multiple depigmented atrophic scars gave the chronically sun-exposed skin a mottled appearance. Although no true sclerosis was noted, the involved skin had a somewhat acrosclerotic appearance, with a pinching of the nose and a furrowing of the lips.

TABLE 3.—*Clinical Comparisons*

	Idiopathic Epidermolysis Bullosa Acquisita	Porphyria Cutanea Tarda
Primary Lesions	Bulla & undue vulnerability to even mild trauma	Bulla & undue vulnerability to even mild trauma
Location	Any portion of body, usually in areas exposed to chronic mechanical trauma	Limited to areas of chronic light exposure
Symmetry	Often asymmetrical (due to accidental trauma)	Usually symmetrical (may have linear pattern due to scratching)
Scarring	May have superficial scarring	May have superficial scarring
Palms—soles	Lesions may be present	No lesions
Knees	Often affected	Seldom affected
Nails	May be dystrophic	Normal
Associated skin findings	None	Limited to sun-exposed areas: (1) melanosis, (2) hypertrichosis, (3) cutis rhomboidalis, (4) mask-like expression, (5) sclerodermoid appearance, (6) hair pigment change (7), morphea, (8) diffuse scleroderma, (9) injection of conjunctiva, (10) hydroa aestivale, (11) photosensitivity
General signs & symptoms	None	May have photophobia, lassitude, itching, evidence of liver disease, diabetes, syphilis
Precipitating factors in formation of lesions	Trauma	Sunlight, trauma, alcohol, (pregnancy and barbiturates not so important)
Urinary and/or fecal porphyrins	Normal	Elevated

The nails and unexposed skin appeared normal.

In addition to the clinical differences between these two patients, our studies revealed other differentiating features. Microscopic examination of the clinically abnormal skin in both patients showed subepidermal bullae. The intraepidermal extension of the blister in the porphyria case was probably a secondary change. Festooning of the base of the bullae emphasized by other workers was not seen in our sections.[11-13] Destruction of the basement membrane, vascular proliferation, perivascular infiltration, and edema of the upper corium, apparently pushing aside the elastic fibers, were much more marked in the tissue from the patient with idiopathic acquired epidermolysis bullosa. In the porphyria sections, endothelial proliferation and marked thickening of the blood vessel walls, due to the presence of periodic acid-Schiff-positive, diastase-resistant material were prominent.

More interesting, however, were the histologic changes in the clinically normal skin of these two patients. Mild subepidermal edema, some vascular dilatation and proliferation, and minimal perivascular infiltration were present in Case 1 (EBA). The most striking feature was the change in the epidermal basement membrane, which was indistinct throughout, and disrupted in several areas associated with subepidermal cleft formation. Our findings suggested that an alteration of epidermal-dermal cohesion, reflected by the basement membrane change, was essential to blister formation and skin fragility in this patient. Whether this process was primary, or secondary to vascular or toxic influences, could not be determined. It should be noted that the role of the basement membrane in binding the epidermis and dermis has not been established.[14,15] In support of the findings of Wise and Lautman, and others, the elastic tissue was intact in the normal skin, and was apparently only secondarily involved in the clinically abnormal tissue in this case.[16,17]

The clinically uninvolved, but pigmented, skin of the forearm of our patient with porphyria cutanea tarda was normal histologically, except for the marked thickening of the dermal blood vessel walls due to homogenous, bright-staining, periodic acid-Schiff-positive, diastase-resistant material. This finding will be discussed presently.

Porphyrin excretion studies, of course, are an essential diagnostic procedure in patients suspected of having porphyria. Both urinary and fecal porphyrin levels were normal in our case with idiopathic acquired epidermolysis bullosa. Large amounts of uroporphyrin, and, to a lesser extent, coproporphyrin, were present in the urine of our patient with porphyria cutanea tarda, and fecal porphyrin studies were considered unnecessary.

A recent report of high urinary zinc levels correlated with acute attacks in intermittent and mixed hepatic porphyria states, plus dramatic results with chelation therapy, prompted us to make similar studies.[18] Case 2 (PCT) had normal levels of zinc in his urine on repeated examinations, despite the activity of his disease. He did improve clinically with the edathamil therapy. The cyclic nature of the disease precludes any definite conclusion as to the efficacy of the treatment. However, it may be that patients with porphyria are abnormally vulnerable to zinc poisoning, and even normal amounts of zinc could lead to the relatively mild clinical changes noted in our case. It should be emphasized that the role of zinc in hepatic porphyria is not established.

Interestingly, zinc excretion in Case 1 (EBA) was definitely elevated. Edathamil therapy had no effect on this clinical course of his disease, despite marked zinc chelation. Zinc is an important constituent of several metalloenzymes, and is essential to many metabolic functions, including maintenance of the integrity of the skin.[19] Whether the increased zinc excretion in our case represented a systemic excess of the metal was not established. Inhibition of certain enzymatic and hormonal activities has been reported with zinc toxicity.[19,20] On the other hand, increased zinc excretion could reflect a degradation of certain zinc-containing enzymes, and actually lead to a zinc-deficient state.[10] If this latter concept were true in our patient, further chelation would not only be ineffective, but might aggravate the process. Naturally, no conclusions can be drawn from the findings of one case, especially since high urinary zinc levels may be found in many unrelated conditions.[21] However, further investigations of the role of zinc and other trace metals in epidermolysis bullosa states are indicated.

As would be expected, the photopatch tests were negative in Case 1 (EBA). The lesions of idiopathic acquired epidermolysis bullosa and of epidermolysis bullosa hereditaria are essentially unaffected by sun exposure.

Though the role of sunlight is poorly understood, it apparently plays an important part in the clinical changes noted with porphyria cutanea tarda. The photosensitizing properties of uroporphyrin, as well as those of synthetic hematoporphyrin have been established.[22,23] It has been suggested that the light sensitivity in cases of porphyria depends on the presence of uroporphyrin I.[13] Large amounts of this substance are present in a free state in the extremely photosensitive erythropoietic type, and at least partly in a zinc complex in the cutanea tarda form, which is less light-sensitive. In the nonlight-reactive acute intermittent porphyria, the porphyrins are present chiefly as precursors. Despite the apparent importance of light exposure in porphyria cutanea tarda, reproduction of the lesions experimentally is rarely successful.[13,24] Schwartz suggested that a porphyrin protein complex which absorbs wave lengths shorter than 3,000 A. might be responsible for a photo-oxidation reaction.[25] This action spectrum would fall into the usual phototoxic range. However, most investigators feel that the action spectrum should be near 4,000 A. because porphyrins, regardless of their side-chains, characteristically absorb these rays.[26] In support of this concept, Wells and Rimington produced an edematous inflammatory reaction in their case with wave lengths around 4,000 A.[27] We were unable to produce any abnormal reactions in our patient, despite high intensity and repeated exposures to wave lengths between 2,500 and 50,000 A. This lack of

response was not unexpected, since our patient had never noted a direct relationship between sun exposure and his lesions, though they were confined to chronically sun-exposed skin.

We have already emphasized the importance of trauma to bulla formation in idiopathic acquired epidermolysis bullosa. It may well be considered an integral part of any definition of epidermolysis bullosa. However, production of bullae by controlled experimental injury is not always possible, especially in the so-called Cockayne-Weber type.[28] Reproduction of the effective form of injury is essential, at least in some of these cases. Blister formation usually followed prolonged pressure in our case, though denudation of large areas resulted from more violent injury. It is interesting that we could not produce bullae by repeated heavy stroking with a blunt instrument. The explanation for this is not clear.

Although spontaneous bullae do occur in porphyria cutanea tarda, the importance of trauma cannot be underestimated. The chronically sun-exposed areas of these patients are unduly vulnerable to even the mildest injury. This property was emphasized by the findings in Case 2 (PCT). Trauma with a blunt instrument showed that the skin on the dorsa of his hands was markedly more fragile than in Case 1 (EBA). As in Case 1, however, we could not produce a blister.

Recently Holti and his co-workers postulated that the fragility and bulla formation of the skin were the results of alterations in the dermal vasculature due to chronic sun exposure. In support of this concept, he noted that histamine and ultraviolet light responses were inhibited in the chronically sun-exposed skin of a patient with porphyria cutanea tarda. In addition, the walls of the superficial blood vessels in these areas were greatly thickened, due to the presence of periodic acid-Schiff-positive, diastase-resistant material.[9] Similar histological changes were seen in our patient with porphyria. Also the histamine responses were inhibited in the chronically sun-exposed skin of the forearms, as compared to the protected skin of the thigh. This is the reverse of the findings of Sonnenschein and Bernstein in a small series of normals, in whom the forearms were generally more reactive than the thighs.[29] This blood vessel injury is perhaps the result of a low-grade phototoxic reaction mediated through the porphyrins. It should be noted that Müller, and Turner and Obermayer, did not find the histamine response inhibited in their studies.[30,31]

Several authors have postulated that alterations in the dermal vasculature are, at least in part, responsible for the changes in both idiopathic acquired and hereditary forms of epidermolysis bullosa.[28,32] Though there were vasodilatation and some thickening of the blood vessel walls, there was no definite evidence for or against this concept in our patient with idiopathic acquired epidermolysis bullosa. The histamine response was normal in this patient.

So far, we have discussed differentiating features and possible mechanisms of the clinical changes in these two patients. There remains the question of etiology.

As the name implies, we have not established an etiology for our case of idiopathic acquired epidermolysis bullosa. A systemic disease may be present to account for the clinical picture as well as the altered zinc excretion. In addition, the possibility that this patient has a tardive inherited disorder must be considered.[33] Perhaps further observation will shed more light on this process.

Porphyria cutanea tarda hereditaria represents an inborn error of pyrrol metabolism, apparently inherited as a dominant trait.[9] Waldenström has also described an acquired form secondary to hepatic damage, frequently due to chronic alcoholism, or, rarely, liver-cell adenomas.[34] Whether the disease of Case 2 was of a hereditary or acquired nature is difficult to say. The patient has a slight increase in sulfobromophthalein retention, suggesting some slight liver damage, and urinary porphyrin studies on his parents and children were

negative. Unfortunately, we have been unable to examine the fecal porphyrin excretion on his family, and evaluation of the hereditary status is not complete as yet.

Summary

Comparison of two patients, one with idiopathic acquired epidermolysis bullosa and the second with porphyria cutanea tarda, revealed several distinguishing features. The skin changes, consisting of bullae, abrasions, superficial scar formation, and milia, were similar in each. However, the lesions in the former were located chiefly on the pressure areas of the extremities, excluding the palms and soles, and were always post-traumatic. The changes in the patient with porphyria were confined to chronically sun-exposed skin, and bullae appeared spontaneously as well as following injury.

Though photopatch tests were negative in both patients, the exposed skin of the patient with porphyria cutanea tarda was extremely vulnerable to trauma. In addition, histamine flare responses were markedly inhibited in these areas. No such localization of skin fragility was noted in the patient with idiopathic acquired epidermolysis bullosa, and his histamine reactions were normal.

The most striking histologic feature in the case with idiopathic acquired epidermolysis bullosa was the disruption of the epidermal basement membrane in the clinically normal as well as the abnormal tissue. In our patient with porphyria, the vascular changes were most prominent.

As would be expected, porphyrin excretion was elevated only in the patient with porphyria. In contrast, zinc excretion was abnormal in the patient with idiopathic epidermolysis bullosa, and normal in the porphyric.

The significance of these findings, as well as the effect of chelation therapy, is discussed.

450 Sutter St.

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Abstract of Discussion

DR. LOUIS A. BRUNSTING, Rochester, Minn.: The authors have pointed out the similarities and differences between the tardive type of epidermolysis bullosa acquisita and porphyria cutanea tarda. Actually, the similarities are limited to three things: first, the inherited trait, the nature of which is not clearly identified in either instance; second, the onset in adult life, and, third, the vulnerability of the skin to trauma, with the production of subepidermal blisters.

The authors have also tabulated important differential features. In porphyria cutanea tarda, because the major changes in the skin occur on the light-exposed areas, sensitivity to light has been suspected but not proved. Such was the case here. In this disease, blistering may not appear at all, and, when it does, it is usually of mild degree, although there are exceptions. The dorsum of the hands may be marked by ecchymotic areas and erosions which become secondarily infected. However, the nails are normal.

There is more to porphyria cutanea tarda than blistering. A violaceous suffusion of the skin of the upper head, neck, and trunk, similar to that seen in individuals with hypertension or Cushing's syndrome, is an unexplained phenomenon. Melanosis and hirsutism are sometimes presenting signs of the disorder in women. Sclerodermoid changes occur often in the reddish-complexioned.

Foremost of the contributing factors of porphyria cutanea tarda is an insult to the liver, and foremost among the insulting agents is alcohol, in the form of spirits, wine, or beer. Even a small amount of this toxin may be sufficient to provoke or maintain symptoms in susceptible persons. In the milder cases, clinical recovery ensues when a program of treatment or protection of the liver is carried out.

Histologically, the authors have confirmed the morhologic and tinctorial changes reported in the walls of the smaller blood vessels of the dermis in porphyria cutanea tarda. The nature of these changes, which show up bright red with the periodic-acid-schiff stain, is not clear. The histopathologist has not been able to explain the blistering of epidermolysis bullosa acquisita on the basis of tissue alteration, in the basement membrane or elsewhere, or on the absence of elastic tissue. If the cohesive force, which normally binds epidermis and dermis, is mediated by enzymes under genetic control, it is reasonable to believe that when this mechanism is disturbed, as in the two conditions under discussion, fragility of the skin develops and blistering may follow.

The diminished flare noted here with the injection of histamine in the sun-exposed skin of the patient with porphyria is undoubtedly related to vascularity. We have noted that when the suffused skin of the upper trunk in such patients is tested by the injection of histamine or by the inunction of Trafuril (tetrahydrofurfuryl nicotinic acid ester), the wheal and the resulting flare are greatly enhanced.

Peters and his group at Madison, Wisconsin, have been carrying out interesting work on the excretion of zinc and copper in patients with various forms of porphyria after edathamil (EDTA) chelation. When edathamil is given intravenously, it is one thing; when it is given by mouth, only about 5% of it is absorbed through the gut. Some favorable influence of such treatment on the symptoms of the acute intermittent type of the disease has been observed, while the results in the more chronic form, such as in porphyria cutanea tarda, are less evident.

The porphyrins themselves are not influenced by chelation. It is interesting to note here that the excretion of zinc in a patient with epidermolysis bullosa acquisita is increased. This needs to be confirmed. Until our knowledge of metallic complexes and trace metals, and their role in metabolism in general, is clarified, specific conclusions about their relationship to diseases of the skin are hardly justified.

DR. STURE A. M. JOHNSON, Madison, Wis.: Dr. Epstein has used chelation therapy to try and make new clinical and biochemical observations in two rare skin diseases. His observation regarding the increase in zinc output in one disease and not in the other prompts me to say a few words.

The role of various trace elements in disease is fascinating and is the thought behind some of the research work being carried on by us at this time. We know that zinc added to the diet of swine will help cure porcine parakeratosis, that it is higher in the unaffected than in the adjacent affected skin of the psoriatic patient, and is found in increased quantities in the urine of patients with porphyria, acrosclerosis, and sarcoid disease during chelation with edathamil. The urinary output of zinc may increase twenty-fold, and this tends to drop to normal amounts as there is clinical improvement. One wonders whether or not this is the only trace element which is involved. How about lead, magnesium, or copper?

It is through our studies on tryptophan loading of patients, and through determining the quantities of its metabolites in the urine, as well as trace elements before, during, and after chelation, with or without pyridoxin, that we have been able to make observations which should lead to a better understanding of the biochemical abnormalities which appear to exist in diseases like acrosclerosis, porphyria, or sarcoidosis. For instance, we note that certain enzyme complexes or systems in which trace metals play a part seem to be corrected by chelation, probably due to the creation of a normal situation for the necessary trace metals to function by liberating the tissues and organs of abnormal quantities of other metal or metals interfering with the system. These can be zinc, calcium, and so forth.

It also appears that pyridoxin plays a part in the normal functioning of the metalloenzyme system, and it is being given by us almost routinely to patients concurrently receiving edathamil. Furthermore, it is also being given to prevent the oral lesions and seborrheic skin changes of pyridoxin deficiency due to chelation.

Our experience with orally administered chelating compounds has not been as good as Dr. Epstein's. We have seen no clinical improvement following daily oral administration over several weeks, and have observed nausea and diarrhea, necessitating stopping the drug. This has not been observed when the disodium salt was given intravenously.

The idea of studying and treating patients who have epidermolysis bullosa acquisita, or even congenital, during chelation is interesting and one which we shall pursue.

DR. NORMAN N. EPSTEIN, San Francisco: I wish to thank Doctors Brunsting and Johnson for discussing our paper. We realize that the isolated findings reported will have to be confirmed or disproved by further studies. We have to give thought to the fact that if you extract a large amount of zinc from the tissues of people who do not have an excess or are not troubled by it, perhaps you might aggravate rather than help their condition. This needs clarification, too.

I would like to say that the biochemical studies were done in the laboratory of Professor Louis A. Strait, Professor of Biophysics at the University of California at San Francisco.

The Remarkable Tissue Mast Cells

With Observations on Mast Cell Acid Polysaccharides in the Cutaneous Lesions of Urticaria Pigmentosa

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The importance of those remarkable cytological units, the tissue mast cells, has soared in recent years. This paper reviews briefly some of the newer concepts of these cells and reports on the author's experience with histological techniques for the study of mast cell acid polysaccharides in the cutaneous lesions of urticaria pigmentosa.

Some Newer Concepts of Tissue Mast Cells

Although the distribution of mast cells varies from species to species, their characteristic location in warm-blooded vertebrates is the loose fibrillary tissue which surrounds small blood vessels and underlies epithelial, serous and synovial membranes.[1,13] In general, parenchymatous organs are poor in mast cells, a noteworthy exception being the widespread distribution of mast cells throughout the parenchyma of the dog's liver.[1] Urticaria pigmentosa, the lesions of which are featured by agglomerations of mast cells, has been known for many years. Only recently, however, has it been recognized that in some instances the cutaneous lesions are but one segment of a mast cell disease spectrum which may embrace cutaneous, osseous, visceral, and hematopoietic lesions, in various combinations.[17] Mast cells contain histamine and heparin, and there is some evidence to suggest that they may also contain hyaluronic acid.[3,5,20] Serotonin (5-hydroxy-tryptamine) has recently been isolated from mast cells of the rat[6] but as yet there is not any convincing evidence that mast cells in humans contain significant quantities of serotonin. It is generally agreed that the histamine is located in or on the mast cell granules[3,7,10] and most investigators believe that heparin is also located in or on the granules.[3,7-10] Several experimental compounds, one of the best known of which is 48/80 (a polymer of *N*-methyl-homo-anisylamine and formaldehyde[9]), have been shown to liberate histamine from mast cells. It has been postulated that the histamine and heparin of mast cells are commingled, and that histamine liberators free histamine from its union with heparin because they have a stronger affinity for heparin than does histamine.[9] According to this theory, heparin is not lost from mast cells treated with histamine liberators.[9] Other investigators believe, however, that histamine liberators also cause the release of heparin from mast cells.[11] The function or functions of mast cells, plainly speculative in the light of present knowledge, are probably multiple. Among other theories, it has been suggested that they may play a role in the production,[3] uptake, transport, and release of histamine, heparin, or hyaluronic acid,[12] and perhaps serotonin in some species,[6] and that they may be concerned with the repair and maintenance of connective tissues.[13]

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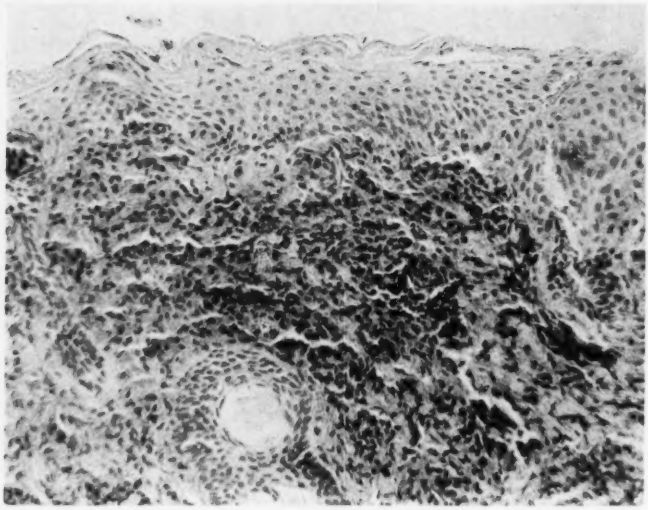

Fig. 1.—Densely packed mast cells in the dermis from a solitary cutaneous lesion of urticaria pigmentosa. Alcian blue-Feulgen stain. Reduced 8% from ×235.

Histological Study of Mast-Cell Acid Polysaccharides

Material and Methods.—Aqueous-formalin*-fixed specimens of involved skin from nine patients with known urticaria pigmentosa (the patients ranged in age from 4 months to 49 years; three of the nine had a solitary cutaneous lesion, and in six the cutaneous lesions were multiple) were sectioned and treated with (*a*) the Alcian blue-Feulgen combination,[14] (*b*) the colloidal iron-Feulgen combination,[14] and (*c*) toluidine blue (comparable sections were subjected to (1) 0.01% toluidine blue without buffer for 10 minutes, (2) 0.01% toluidine blue in 0.01 M HCl-sodium citrate buffer measured at pH 3.3 for 30 minutes, and (3) digestion for 18 hours in 0.2% testicular hyaluronidase in 0.1 M, pH 6.0 acetic-sodium acetate buffer at 37 C followed by staining for 30 minutes with 0.01% toluidine blue in 0.01 M, pH 4.0 HCl-sodium citrate buffer[18]). Although aqueous formalin is reputedly not the ideal

* Solution used: Aqueous formalin (10%).

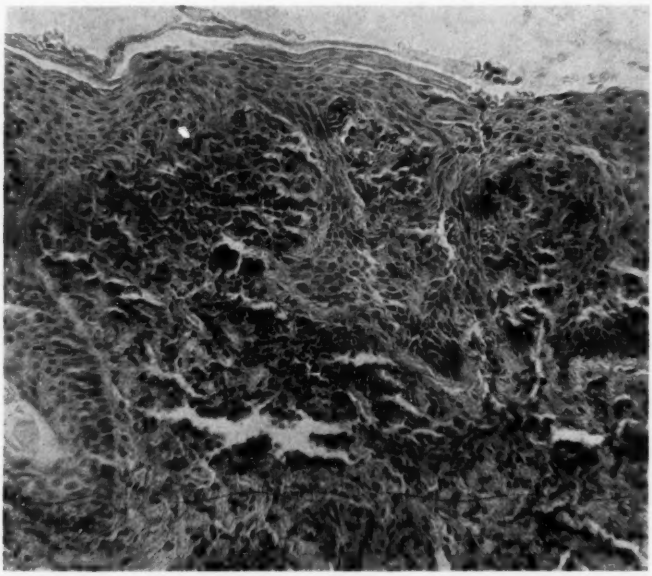

Fig. 2.—Mast cells in the dermis from the same case as Figure 1. Colloidal iron-Feulgen stain. ×235.

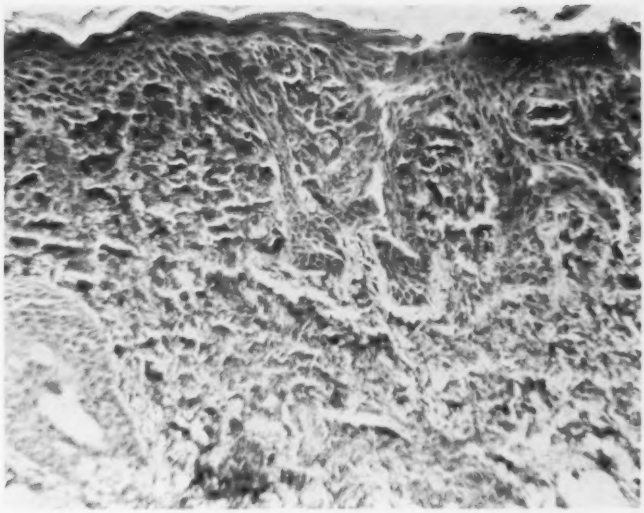

Fig. 3. — Mast cells in the dermis from the same case as Figure 1. Unbuffered toluidine blue stain. Reduced 8% from × 235.

fixative for mast cells [15] because of possible solubility of the metachromatic material, the granules, or both, in water,[20] it proved itself serviceable in this study, as it has for other investigators.[16]

Observations.—(*a*) Treatment of sections of urticaria pigmentosa with the Alcian blue-Feulgen combination,[14] followed by immersion in picric acid for background contrast, stained mast-cell nuclei (and other nuclei) magenta and the granules bluish-green, against a yellow background of epidermis and dermis (Fig. 1).

(*b*) Treatment of sections of urticaria pigmentosa with the colloidal iron-Feulgen combination,[14] followed by immersion in picric acid for background contrast, stained mast-cell nuclei (and other nuclei) magenta and the granules a bright bluish-green, against a yellow background of epidermis and dermis (Fig. 2). The over-all results achieved with the colloidal iron-Feulgen combination, were quite similar to those with the Alcian blue-Feulgen combination, except for the fact that the colloidal iron-Feulgen combination stained mast-cell granules more intensely.

(*c*) Treatment of sections of urticaria pigmentosa with unbuffered toluidine blue stained mast-cell nuclei blue and the granules a reddish-purple hue, against a bright blue background of epidermis and dermis (Fig. 3). When comparable sections were treated with buffered toluidine blue, on the other hand, mast cells were stained in approximately the same fashion, but the background of epidermis and dermis was pale blue, resulting in much sharper contrast between mast cells and other structures. Treatment of sections of urticaria pigmentosa with testicular hyaluronidase prior to staining with toluidine blue showed that practically all of the mast-cell granules resisted enzyme extraction.

Comment

Of the multifarious polysaccharides, which comprise a major subdivision under the heading of carbohydrates, at least one (heparin), and possibly a second (hyaluronic acid—both heparin and hyaluronic acid are acid polysaccharides), is present in mast cells. Although heparin, an amino sugar-containing acid polysaccharide, has been studied intensively, its complex structure is still not thoroughly understood.[19] It appears, however, to be a polymer of disaccharide units comprised of glucuronic acid and an amino sugar, glucosamine, resembling hyaluronic acid in its makeup.[1] The amino sugar of heparin is sulfated, however, whereas that of hyaluronic acid is acetylated.[1] The cutaneous lesions of urticaria pigmentosa were selected for this histological examination of mast-cell acid polysaccharides because of the availability and accessibility of the lesions and because of the numbers of mast cells usually found in such lesions. It is recognized, however, that the mast cells of urticaria pigmentosa may not be comparable in all respects to "normal" mast cells, and that observations on mast-cell acid polysaccharides in the cu-

taneous lesions of urticaria pigmentosa may not be equally applicable to "normal" mast cells.

There is good evidence that the coloration of acid polysaccharides by toluidine blue is contingent on binding of the dye by acid groups of carbohydrates, and that the resulting metachromasia stems from a change in the absorption spectrum of the blue dye, imparting a reddish-purple hue to the sites of acid polysaccharides.[14] Toluidine blue may also be bound by acid groups (presumably phosphoric) of nucleic acids, however, thereby interfering with the selective staining of acid polysaccharides, especially if the amount of nucleic acids is large or that of acid polysaccharides is small.[14] A potentially significant advantage of colloidal iron and Alcian blue over toluidine blue for the coloration of acid polysaccharides is the fact that they stain acid polysaccharides almost exclusively,[14] with little or no tendency to stain ribonucleic acid, which is so often present in the cytoplasm of cells. Furthermore, since the staining achieved with both colloidal iron and Alcian blue is virtually limited to acid polysaccharides, and has little tendency to fade on exposure to other histological reagents, colloidal iron and Alcian blue can be combined with other informative staining methods, such as the periodic-acid-Schiff and the Feulgen reactions,[14] thereby enhancing their field of applicability.

Observations noted in the course of the investigational portion of the present study showed that mast-cell granules were well stained by Alcian blue, colloidal iron and toluidine blue. The colloidal iron-Feulgen combination stained mast-cell granules more intensely than did the Alcian blue-Feulgen combination, but the granules were not as sharply demarcated from other structures with either the colloidal iron-Feulgen or the Alcian blue-Feulgen combinations as they were with toluidine blue. (The Feulgen reaction, which is highly specific for nuclei, leaving other structures unstained, was utilized in the present study solely as a counterstain, in combination with colloidal iron and Alcian blue, resulting in sharp contrast between the magenta nuclei and the bluish-green granules of mast cells.) Good metachromatic staining of mast-cell granules by dilute toluidine blue at a fairly low pH, as observed in the present study, is consistent with the presence of a sulfated acid polysaccharide, probably heparin.[18] Resistance of the granules to extraction by testicular hyaluronidase, on the other hand, supports the view that the acid polysaccharide was neither hyaluronic acid nor the usual types (A or C) of chondroitin sulfate.[18]

Summary

Data assembled in the course of the present investigational study on mast-cell acid polysaccharides in the cutaneous lesions of urticaria pigmentosa suggest the presence of heparin, rather than hyaluronic acid or the usual types of chondroitin sulfate, in or on the mast-cell granules, and support the view that colloidal iron and Alcian blue have certain advantages which make them promising tools for the further study of acid polysaccharides in tissue sections.

The authors thank Dr. Marcus R. Caro, Dr. Julius E. Ginsberg, Dr. Hermann Pinkus, and Dr. Frederick J. Szymanski, who furnished some of the tissue specimens used in this study.

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ABSTRACT OF DISCUSSION

DR. WALTER B. SHELLEY, Philadelphia: I always enjoy a paper by Dr. Cawley, and this experience has been no exception.

Dr. Cawley divided his paper into two parts: the historical review of concepts, and, secondly, a summary of his histological observations. I will do similarly in my discussion.

There are a few additional new concepts that have come out in regard to mast cells that, I think, bear attention here. One of them is that, recently, in animal experimentation, it has been possible to show that antibodies may develop against mast cells, so that we must consider, in our theories concerning skin diseases, that autoimmune mechanisms may take place in regard to the mast cell, and that this might explain certain characteristics of the course of the disease in urticaria pigmentosa, or possibly may have something to do with unexplained examples of urticaria itself.

The second point that has come out more recently in regard to the mast cells is the fact that these granules (which, Dr. Cawley has pointed out, contain histamine and heparin) after release by the cell at times of injury, may be engulfed by other cells, so it is difficult cytologically to tell always whether one has, with regard to a specific cell, a mast cell or a phagocytic cell.

The most interesting recent contribution in this area, I think, is the fact that the eosinophil itself may engulf the mast-cell granules, and these may be found in the cell body as a basophilic material. It has been puzzling to people as to what this material was, but it is now recognized that it is actually phagocytosed mast-cell granules.

The third point in regard to the literary review that I would like to bring up is the fact that Dr. Baer and his collaborators have recently shown that reserpine has an interesting therapeutic effect in patients with urticaria pigmentosa. As you know, reserpine releases serotonin; it is a serotonin releaser. As Dr. Cawley has pointed out, the mast cell in man does not contain serotonin. It is one of those examples where you have to study the human subject to know specifically what is going on in that area. You cannot transfer data over from animals. We have, then, this interesting observation of Dr. Baer, that reserpine has an effect on urticaria pigmentosa, and yet, the key cell in this disease, the mast cell, has no serotonin.

I would suspect that, possibly, release of serotonin from other cells and elsewhere in the body is having a secondary effect on the mast cell. Asboe-Hansen showed that serotonin causes histamine release or degranulation of the mast cells, so I think there may be a sequence of events taking place in the work that Baer has reported.

Now, to turn to the histological part of Dr. Cawley's presentation, I think that this paper has been very aptly entitled, "The Remarkable Tissue Mast Cell." This mast cell is remarkable, historically, in regard to staining. The mast cell was discovered by Ehrlich 80 years ago. He used it as a test object for the development of two basic principles in histologic staining. One was the fact that he recognized that the material in the mast cell, the granules, is acidic, and, secondly, he recognized that it was so acidic or so unique that it caused a change in the color of the dye that was used to stain this cell; in other words, he discovered metachromasia as a result of observing the mast cell.

The chemistry was unknown, and it took 50 years before Ehrlich's observations could be interpreted in modern chemistry. Then, it was found that heparin was responsible for this acidic reaction in the mast cell. Because of the acidity of this sulfated carbohydrate, one has the explanation for the stain that Dr. Cawley has described here. Alcian blue is a basic stain, and is attracted to the material in the mast-cell granule.

It is of interest that Dr. Cawley has presented for the cytologists and pathologists a new tool, a new technique, which is more specific, apparently,

in demonstrating heparin in contradistinction to the other acidic substances which we find in cells.

I have just two questions for Dr. Cawley. One is, I would like to know if he has been able to see a difference in the staining characteristics of different examples of urticaria pigmentosa; that is, in regard to the possibility that there are different clinical types that might be revealed by the stain. Secondly, has he done any supravital staining of the mast cell in the living subject?

DR. HAMILTON MONTGOMERY, Rochester, Minn.: There are three points I would like to bring up.

First, with regard to formalin fixation, it works perfectly well in 90+% of the cases. There was one case, however, that Dr. Kierland subsequently reported, of a nodular type of urticaria pigmentosa in which I missed the diagnosis because the mast cells did not stain with Wright's stain. The late Fred Weidman pointed out, at the time the case was presented at the Clinical Pathology Conference at the American Academy of Dermatology, that oftentimes other metachromic stains might be positive, including polychrome methylene blue, toluidine blue, etc.

The second point is that back in 1926 when Oscar Gans was at the Clinic, we used to divide the biopsy specimen in two, one half being fixed in formalin and the other in absolute alcohol. In cases of urticaria pigmentosa in the absolute-alcohol-fixed sections, stains with mucicarmine revealed the mast cells were laden with mucin.

The third point is that the mast cells are large histiocytes and in so-called histiocytosis-x of Lichtenstein, which includes eosinophilic granuloma of the bone, Letterer-Siwe disease and Hand-Christian disease in children and in infants, besides clinical features seborrheic in nature, one often sees nodular and papular lesions which need to be differentiated from those seen in urticaria pigmentosa. Both conditions have large histiocytic cells and I have in the past made an erroneous diagnosis of histiocytosis-x when, with the use of polychrome stains, the cells were proven to be mast cells of urticaria pigmentosa. The latter condition, of course, gives a much less serious prognosis unless one is dealing with the systemic form of the disease, namely with a mastocytoma.

DR. LOUIS H. WINER, Beverly Hills, Calif.: Dr. Asboe-Hansen uses 4% aqueous lead acetate as a fixative for demonstrating mucin in mast cells. I have recently used this type of fixation, and I have had, in my first batch of about a hundred slides, difficulty in getting rid of the crystals of lead acetate. I subsequently asked my technician to immerse these specimens in distilled water overnight to remove these crystals of lead acetate, and have now obtained sections free of crystals.

DR. WALTER R. NICKEL, San Diego, Calif.: I would like to add my compliments with the others on the paper by Dr. Cawley. Because of my interest in urticaria pigmentosa—in fact, it was my initial paper before this group—I had cited cases of mastocytosis without pigmentation. I do not believe I included one unusual manifestation, which was brought to my attention forcefully last week in Philadelphia. Captain Lockwood, at the Naval Hospital, had written to me about a young adult man, whose slides I was able to review.

This man had a generalized erythroderma, without any pigmentation whatever, and had typical disseminated mastocytosis present in several biopsies from different areas. A good many of you men saw this patient at the Atlantic Dermatological Society, where they presented him.

I would therefore like to conclude by saying that any case of generalized erythroderma, in which the diagnosis is not obvious, with or without pigmentation, certainly would deserve special staining for mast cells.

DR. FRANK E. CORMIA, New York: A number of years ago, when we were interested in differentiating between clear and dark cells in sweat glands, we noticed a considerable variation of the toluidine blue stain in the number of mast cells in apparently normal individuals. It seems to me that possible anatomical differences in the number of these cells in various individuals may explain some of the unknown factors in the development of urticaria, particularly traumatic urticaria. It would be of interest to do a special study on a large number of such patients.

DR. RUDOLF L. BAER, New York: Dr. Shelley mentioned the publication by Dr. Bersani, Dr. Pelzig, and myself on the effects of reserpine in urticaria pigmentosa. Since we submitted that report, we have hospitalized several patients and have done biopsies before, and again one week after giving them reserpine.

One of these patients was among the three in the original report; the improvement in this 13-year-old girl has been maintained. However, the additional patients whom we hospitalized did not show any improvement under reserpine treatment within the period of our observation.

We did not find 5-hydroxy-indole acetic acid, the urinary excretion product of serotonin, in the urines of these patients. This, of course, is in conformance with the reports that the mast cell in man, contrary to the mast cell in rats and in certain other species of animals, does not contain 5-hydroxytryptamine.

Urticaria pigmentosa is a most fascinating disease. Some ten years ago, I saw a man in his fifties who had developed urticaria pigmentosa two years before. Seven years after I had seen him, he was operated on for an intestinal adenocarcinoma, and, six months after that, the urticaria pigmentosa disappeared.

I think, to speak dermatologically, that in urticaria pigmentosa, we have not yet scratched the surface.

DR. EDWARD P. CAWLEY, Charlottesville, Va.: I thank all the discussers.

In answer to Dr. Shelley's question about the difference in staining qualities of the mast cells in different varieties of urticaria pigmentosa; as nearly as we have been able to determine, they all stain in the same fashion.

Recurrent Oral and Cutaneous Infections Associated with Cyclic Neutropenia

FREDERIC T. BECKER, M.D.; WILLIAM D. COVENTRY, M.D., and JAMES L. TUURA, M.D., Duluth, Minn.

Recurrent skin and mucous membrane infections, occurring at regular intervals, should alert the clinician to the possibility of an unusual hematologic disorder known as cyclic or periodic neutropenia.

This disease is characterized by a cyclic depression of neutrophils, occurring at intervals of 12 to 30 days (average 21 days) lasting from 5 to 8 days and accompanied by fever, malaise, and infections occurring in the skin and mucous membranes. The neutrophils in the peripheral blood regularly fall to low levels or disappear at this time. Between the periods of depression, the neutrophils increase but seldom rise to above 50% of the total. The leukocyte count is usually in the low normal range (4,000 to 5,000).

The literature describing this rare disorder will be reviewed in this paper, and three cases will be reported. These cases are of particular interest, since a long period of observation (10 and 12 years) was afforded in two instances, and the third, an infant of one of these patients, died at the age of seven weeks of sepsis, pyoderma, and agranulocytosis.

Review of the Literature

Cyclic neutropenia was first described by Leale in 1910.[1] Reiman,[16] in 1949, reviewed the 16 published cases of this malady and considered this a specific entity and included it in his classification of "periodic diseases." Page and Good,[33] in 1956, added 7 cases. A total of 33 cases have now been reported in the literature (Table). We are adding two more cases; the third was previously reported.[32]

A few authors [8,11,31] relate cyclic neutropenia to hormonal disturbances, since some patients experience improvement during pregnancy while others have exacerbations at such times. Symptoms in other patients have had their onset following parturition, and in some they occur with onset or are associated with menstruation. The multiplicity of clinical manifestations is suppressed by steroid administration,[22,23,28,30] yet these drugs produce no effect on the cyclic alteration of the neutrophil count. Despite many instances suggestive of endocrine dysfunction, no consistent hormonal imbalance has been verified.

Several investigators have considered cyclic neutropenia to represent a form of "hypersplenism" because of the presence of splenomegaly in some patients. Splenectomy results in a temporary alteration in the cyclic depression of the neutrophils and moderate improvement in symptoms. However, after operation the periodic cycle of the neutrophils usually returns. Those who have had a splenectomy have experienced some reduction in the severity of their infections. Duane,[25] after a review of 13 cases in which splenectomy had been performed, indicated that this procedure would most likely be beneficial in the older patients with enlargement of the spleen. He agrees with Coventry [32] in that little benefit could be expected if the patient were under 25 years of age and if the spleen were normal or only slightly enlarged.

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From the Department of Dermatology, The Duluth Clinic (Dr. Frederic T. Becker and Dr. James L. Tuura) and the Department of Internal Medicine, The Duluth Clinic (Dr. William D. Coventry).

Summary of Thirty-Three Cases of Cyclic Neutropenia

Case	Symptoms	Bone Marrow	Age	Sex	Duration	Cycle Length, Days	Hormone Excretion	Treatment	Spleen Removed	Splenectomy Results or Remarks
1. Leale[1] Rutledge[2] Thompson[3]	Fever, stomatitis, lymphadentitis	None	25	M	Since infancy	21	Female type of hormone excretion	Autogenous vaccine	—	Patient's serum decreased the motility of normal leukocytes. Symptomatology better after age 30; died of pneumonia, age 34
2. Sutton[4]	Fever, stomatitis	None	16	M	Since infancy	21	----------	----------	—	No blood cell counts taken on proven case
3. Doan[5]	Fever, skin ulcers, stomatitis	None	18	F	Not given	21	Unrelated to menses	Pentose nucleotide	+	Symptomatic relief, but continued cycles with a higher WBC level
4. Embleton[6]	Fever, stomatitis, malaise	None	43	F	--------	17-19	Unrelated to menses		—	
5. Imerslund[7]	Fever, stomatitis, malaise	Many precursors, no mature forms	16	M	Since infancy	21	No abnormality in female hormones		—	
6. Barsby[8]	Fever, stomatitis, arthralgia, abdominalgia	Hypoplastic marrow changes before blood	41	F	--------	21-28	Questionable relation to menses	Pentose nucleotide, yellow bone marrow, liver, iron, niacin, estrogen	—	
7. Vahlquist[9]	Fever, skin abscess, otitis media	Hypoplastic	4	F	Since age 2 months	21	----------	Pentose nucleotide		
8. Reznikoff[10]	Fever, abdominalgia	Hypoplastic	18	M	Since infancy	21	Female hormones normal, 17-Keto, low at onset	Adrenocortical extract ineffective	+	Symptomatic relief, bone marrow count increased, peripheral blood unchanged; patient's serum inhibited rabbit bone marrow cells
9. Barling[11]	Fever, stomatitis, vulvar ulcers when pregnant	None	32	F	Since age 12	21-28	Persistence of ulcers when pregnant		—	
10. Loffler[12]	Fever, arthralgia, lymphadentitis	Many precursors, no mature forms	30	M	One year	21	----------	----------	+	No benefit, spleen showed inflammatory hyperplasia
11. Owren[13]	Fever, stomatitis	Hypoplastic marrow before blood changes	23	M	Five years	20	----------	Pentose nucleotide	+	No benefit, spleen enlarged with nonspecific reactive changes
12. Fullerton[14]	Fever, local infection, malaise, tonsilitis	Hypoplastic marrow before blood changes	62	M	One year	23-28	Normal female hormones and 17-ketosteroids	Diphenhydramine pyridoxine	+	Symptomatic relief, cycles continued at a higher WBC level, spleen enlarged with hyaline degeneration of central arteries

13. Erf [15]	Fever, stomatitis	Hypoplastic	55	F	Two years	28	----------	----------	+	Symptomatic relief, steady fall in WBC count after an initial rise, reticular hyperplasia of spleen; not a recognized case
14. Alt, cited by Reimann [16]	Fever, stomatitis	----------	18	M	Since infancy	18-22	----------	----------	—	
15. Reimann [16]	Fever, stomatitis, arthralgia, lymphadenitis	Hypoplastic	23	M	Five years	21	Normal female hormones, 17-ketosteroids and corticotropin response	Yeast, liver, bone marrow	—	
16. Cobet [17]	Fever, stomatitis, depression	----------	25	F	Since infancy	21	Unrelated to menses	----------	+	Symptomatic relief, no change in blood picture, normal spleen
17. Borne [18]	Fever, local infection	Hypoplastic marrow before blood changes	3	F	Since age 5 months	21	Small amounts of estrogen and gonadotropin at onset of attacks—absent between attacks	Pentose nucleotide, vaccine	—	
18. Rolland [19]	Fever, stomatitis, lymphadenitis	Many precursors, no mature forms	8	F	Since age 7 months	21	Normal female hormones	----------	—	
19. Sandella [20]	Fever, stomatitis, malaise	Hypoplastic	64	F	One year	20-22	----------	----------	+	Symptomatic relief, blood cycles lengthened, reticular hyperplasia of spleen. Died 16 months later from lymphosarcoma
20. Moncrieff [21]	Fever, sore throats	----------	2	M	--------	--	----------	----------	—	Cured by tonsillectomy, not a well-documented case of cyclic neutropenia
21. Monto [22]	Fever, stomatitis	Hypoplastic	77	M	One year	21	----------	Corticotropin dramatic results	+	Symptomatic relief, constant neutropenia followed an initial neutrophilia; sclerosis of central arteries, mild
22. Siguier [23]	Fever, sialorrhea	----------	42	M	Seven years	20	Corticotropin cortisone	Corticotropin cortisone ineffective	—	
23. Good [24]	Generalized infections	Failure of maturation	2	M	Since 7 months	21	----------	----------	—	Associated agammaglobulinemia. Died of pneumonia
24. Duane [25]	Angina, cystitis, perirectal abscess	Maturation arrest	28	F	Nine years	16-29	Not determined; pregnant	Penicillin	—	Pregnant—stillborn. Eosinophilia between neutropenic cycles

Summary of Thirty-Three Cases of Cyclic Neutropenia—Continued

Case	Symptoms	Bone Marrow	Age	Sex	Duration	Cycle Length, Days	Hormone Excretion	Treatment	Spleen Removed	Splenectomy Results or Remarks
25. Magnin, Suits, Wenzel [26]	Fever, angina, recurrent infection	Maturation arrest, normal between	6	M	One year	21-28	Not determined	Penicillin	+	Rise in eosinophils and monocytes during neutropenia. Two years afte. surgery cycle same, less infection
26. Hahnemann [27]	Pneumonia and furunculosis, pharyngeal and oral ulcers	Maturation arrest	14	M	Onset in infancy	18-21	Not determined	Supportive	—	No infections after age 18 years
27. Above authors [27]			2	F	Three months	14 days	Not determined	Penicillin	—	Daughter of above. Gammaglobulin normal; negative agglutinations
28. Chaiken [28]	Aphthae, gingivitis, pharyngitis	Maturation arrest	20	M	Six months	21	Not done	Antibiotics and steroids	—	Intravenous ACTH; no effect on neutrophil cycle
29. Plum [29]	Fever, stomatitis	----------	12	M	Two years	21	Not done	----------	—	Cited by Reiman
30. Natelson [30]	Pharyngitis, aphthae, fever	Normal to neutrophilic hyperplasia	26	F	Five years	15	None	Antibiotics and antihistamines	+	Less depression of neutrophils. Less symptoms; no effect steroids; abdominal nodes showed giant follicular lymphoma
31. Jackson and Merrill [31]	Pharyngitis, aphthae, fever	None	30	F	Two years	28	None	Pentose nucleotide Antuitrun S	—	Associated with onset of menstrual periods
32. Coventry [32]	Furuncles, fever, aphthae	Normal in neutrophilic stage	16	F	Infancy	21	None	Antibiotics, transfusions	+	Infections improved with antibiotics, symptomatology improved with splenectomy; no change in cycle
33. Page and Good [33]	Impetigo, aphthae, fever, furunculosis, malaise, oral ulcers	Maturation arrest	15	F	At age 5 months	21	Repeated F.S.H. and ketosteroid studies normal	Steroids, vaccine, antibiotics, leucocytes	+	Relieved of symptoms for six months; no change in cycle

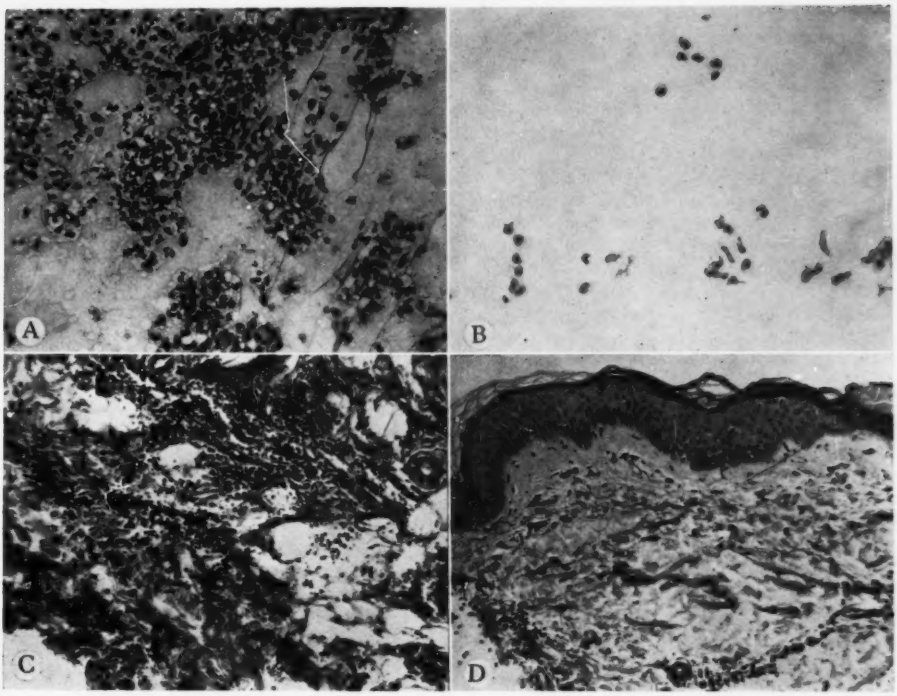

Fig. 1.—Reproduced from Page, Arthur R., and Good, Robert A.: Studies on Cyclic Neutropenia, *A.M.A. J. Dis. of Child.* 94:623, (Dec.) 1957. Inflammatory reaction of the skin in patient with cyclic neutropenia. Compared on this Figure is the cellular reaction of the skin during the neutrophilic phase of the inflammatory cycle, when near-normal numbers of neutrophils are present in the circulation (A), and that during the neutropenic phase of the cycle, when no neutrophils can be found in the blood (B). Shown is the 18-hour stage of the inflammatory cycle induced by skin irritation, Rebuck technique. Note that not only are neutrophils lacking in the exudate but that a comparable hematogenous mononuclear infiltration has also failed to occur. In Part C is illustrated the intense inflammatory response, both polymorphonuclear cells and round cells, observed in the skin biopsy specimen taken 24 hours after injection of typhoid vaccine intradermally during neutrophilic phase of the cycle; × 85. In contradistinction, Part D illustrates the lack of cellular exudate in the inflammatory reaction in a specimen taken 24 hours after injection of typhoid vaccine during the neutropenic phase of the cycle; × 85.

The plausibility of an antibody-antigen reaction as the cause of cyclic neutropenia has been studied. Fullerton[14] and Page and Good[33] transfused blood obtained from their patient during the neutropenic cycle into compatible recipients without observing any depression of the recipient's leukocytes or neutrophils. Page and Good were unable to produce agglutination of normal neutrophils using blood serum taken from their patient during the neutropenic phase. They were also unsuccessful in demonstrating abnormal phagocytosis with their patient's neutrophils obtained during various stages of the cycle. Likewise, serum taken from this patient with periodic neutropenia did not appear to alter the phagocytic activity of neutrophils obtained from a normal donor.

In the few instances[27-33] in which the blood proteins have been studied in this disease, slight increases in gamma-globulin have been observed except in the patient reported by Good and Varco.[24]

Interpretations of bone-marrow studies of these cases vary widely. Page and Good studied the marrow of their patients at varying times during periods of neutrophil

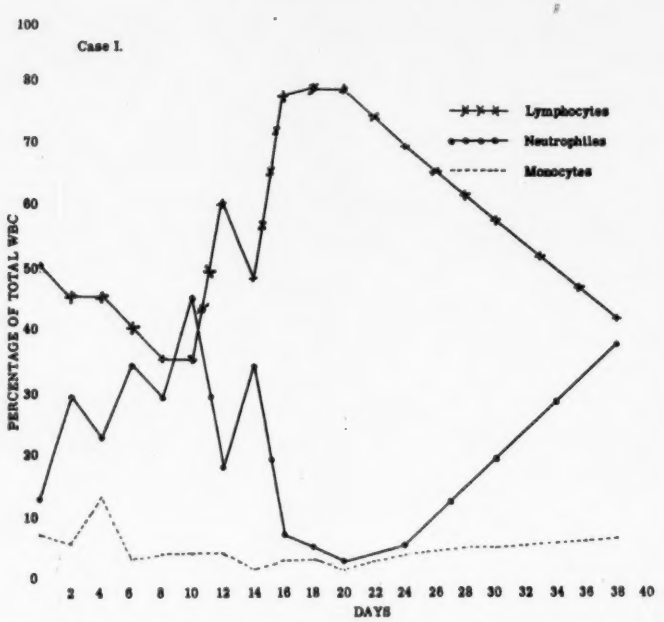

Fig. 2 (Case 1).—Differential WBC over a 38-day period showing the typical cycle of the neutrophils.

suppression and compared them with other specimens taken from the same patient at other periods of the cycle. They found that all marrow specimens taken at the beginning phase of peripheral blood neutropenia showed an absence of myelocytes, metamyelocytes, and mature neutrophils. In addition, the promyelocytes were at their lowest level. Marrow samples taken just prior to the appearance of neutrophils in the peripheral blood contained numerous myelocytes and metamyelocytes, and at that time the promyelocytes were greatly increased. Finally, the bone marrow obtained during the decline of neutrophil count lacked mature neutrophils, myelocytes, and metamyelocytes, and the promyelocytes were at relatively low levels. They concluded that periodic neutropenia was likely caused by some unusual cyclic arrest of production of the entire neutrophilic series and interpreted these findings as a "maturational block" at the promyelocyte stage.

Antibody response to injections of typhoid and paratyphoid vaccine, diphtheria toxoid, mumps, and poliomyelitis virus during periods of neutropenia have been found by Page and Good to be normal. They observed that the production of acute phase serologic reactions (C-reactive protein and elevated sedimentation rate) is not dependent on the presence of neutrophils. The delayed skin reactions with injection of extract of Pseudomonas polysaccharide (Piromen) streptokinase-streptodornase, and typhoid-paratyphoid vaccine are not altered during the patient's neutropenic cycle.

Biopsies of injured skin in Page and Good's (Fig. 1) patient showed abnormal inflammatory response during the neutropenic periods. At this time, there is absence of neutrophils in the exudate along with a distinct absence of mononuclear cell infiltration, and the hematogenous macrophages do not appear. This observation suggests that neutrophilic infiltration, in some way, conditions lymphocytic invasion and macrophage accumulation in a normal inflammatory reaction.

The literature indicates that many types of treatment have been utilized to control the symptoms associated with this disease. Parenteral injections of normal leukocytes and staphylococcal vaccine do not appear to

alter this condition. Steroids do not change the cyclic alteration in blood count but can reduce severity of clinical symptoms. Wide-spectrum antibiotics, given several days prior to any anticipated fall in neutrophils, in most instances have been successful in reducing the severity of the infections at this time. However, Page and Good warn against their indiscriminate use, since resistant organisms tend to develop and are likely to cause persistent infections which are unresponsive to antibiotics.

Report of Cases

CASE 1.—A 33-year-old housewife was first seen in September, 1949, with a history of recurrent "canker sores" dating from childhood. These became more severe four months after the birth of her first child. When initially seen, a diagnosis of periadenitis necrotica mucosa recurrens was made and control by repeated smallpox vaccinations was attempted. Laboratory examination showed WBC 4,700, 33% neutrophils, 56% lymphocytes, 7% monocytes, and 4% eosinophils. This patient was not seen again until 1954, and, at this time, she gave a history of temperature elevations and malaise associated with recurrent oral lesions occurring at approximately three-week intervals. Laboratory work at this time showed WBC 5,300, sedimentation rate 21 mm. per one hour, and agglutination test for Brucella was negative. The patient was treated with chlortetracyclaine lozenges.

She was next observed in 1957 at the age of 40 years with a continued history of recurrent eruptions of the mouth with fever, at times reaching 103 degrees, and dysuria. The latter symptom had increased in severity over the preceding eight years. Physical examination was normal except for presence of subacute gingivitis. Blood examination showed WBC 5,500 with 47% neutrophils, 50% lymphocytes, and 3% monocytes. Urine culture revealed growth of Escherichia coli. Suspicion of cyclic neutropenia led us to conduct serial white blood counts and differential counts; the diagnosis was thus confirmed (Fig. 2). This patient was given instructions to use oral penicillin for approximately three days prior to and during the period of granulopenia. The severity of symptoms has been fairly well controlled by this therapy.

CASE 2.—A 16-year-old girl was first seen three weeks after the birth of her first child, in October, 1948. At this time the patient had an elevated temperature, complained of chills, and had severe furunculosis of the buttocks and inguinal folds. Further examination revealed gingivitis and healed scars of old infections in the region of the buttocks and inguinal folds. Laboratory data: Hb 9.7 gm., WBC 3,850 with 11% neutrophils, 2% eosinophils, 1% basophils, 26% monocytes, and 60% lymphocytes. Rapid improvement followed administration of a blood transfusion and antibiotics. A differential white blood count three days later showed 38% neutrophils and, at the time of discharge from the hospital, on the eleventh day, WBC 6,500 with the neutrophils 60%. A sternal bone-marrow aspiration at this time was normal.

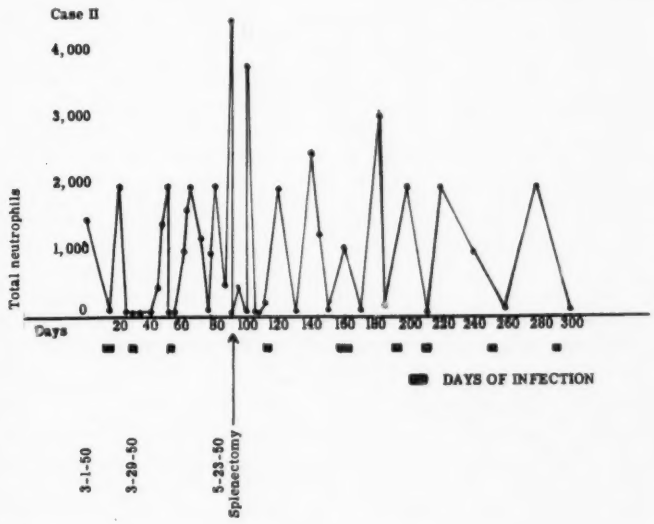

Fig. 3 (Case 2).—Total neutrophil count in thousands over a 300-day period showing temporary alteration after splenectomy. Periods of infection are shown in dark rectangles.

It was subsequently learned that, in 1933, at the age of one year, this patient had severe otitis media with mastoiditis and furunculosis and, while hospitalized, developed severe rectal fissures. After mastoidectomy and cauterization of the rectal fissure, the patient improved. Neutropenia and anemia had been observed at the time of these procedures. From 1933 to 1948, this patient had been hospitalized under the care of many physicians for recurrent oral infections, furunculosis, and multiple abscesses. During all hospitalizations, anemia and neutropenia were noted. The patient's parents and siblings were always in good health. Her only known drug reaction was that of urticaria following a penicillin injection.

This patient was next hospitalized in February, 1949, under our care for the treatment of an ulcer of the buccal mucosa and pyoderma of the right thumb. In April of the same year, she was hospitalized for treatment of a purulent gingivitis and associated cervical adenopathy. During both periods of hospitalization, neutropenia was observed. Antibiotics and local treatment produced prompt improvement.

Over the next 10-month period, the patient was seen for treatment of repeated instances of gingivitis and buccal ulceration associated with elevation of temperature. The leukocyte counts during these periods ranged from 2,800 to 5,400 with the neutrophils being absent for periods of 4 to 5 days on several occasions. Serial white blood cell and differential counts revealed the period of neutropenia to be of 5 to 8 days' duration and the neutrophilic phase 12 to 14 days, thus each cycle with its recovery phase and neutropenic period totaled 17 to 22 days (Fig. 3).

In 1950, a splenectomy was performed, and a 250 gm. spleen was removed. The patient was not seen until 1952 when a re-survey of the leukocyte count and cycle showed an identical fluctuation of the white cell series to that seen prior to splenectomy. However, following this procedure, the infections occurring during the neutropenic periods were not as severe. The patient experienced only a brief episode of pyelitis during her second pregnancy. Serial blood counts were made on this patient's second child and they were found to be within normal limits. In December, 1954, the patient delivered her third child, an apparently normal girl.

Case 3.—A 1-month-old female, the daughter of the above patient. This child was well until January 1955, when she developed cough and swelling about the nose. She was treated with acetylsalicylic acid and intramuscular penicillin. Four days later she was hospitalized because of dyspnea and marked elevation of temperature.

After 3 days (January 26, 1955), she was transferred to St. Mary's Hospital, Duluth, Minnesota, under the care of Doctor R. O. Bergan. Generalized icterus was apparent, temperature was 103.6 F, heart rate was 200, and breathing was stertorous. The nose was red and markedly swelled, and cellulitis extended laterally to encompass both cheeks. Laboratory data: WBC 20,700 with complete absence of neutrophils, 1% eosinophils, 25% lymphocytes, and 74% monocytes. Hb 6.7 gm. and RBC 2.24. Direct Coombs test was negative. Urinalysis: specific gravity 1.014, albumin 3+, and 5-6 WBC per high-power field. The patient was transfused with 120 cc. of whole blood. On the second hospital day, the leukocytes dropped to 6,300 with differential similar to that on admission, exhibiting an absence of neutrophils. Other laboratory data included: direct bilirubin 4.2 mg. %, indirect 2.9 mg. %, and total 7.1 mg. %. Thymol turbidity 3 units per milliliter, and cephalin flocculation test 4+. Cultures from the nasal area showed Pseudomonas organisms, resistant to all antibiotics except streptomycin. Erythrocytes and platelets were normal in the blood smear. Leukocytes were normal except for an increase of granules in the cytoplasm of some of the monocytes. Peroxidase stains were negative. A differential white blood cell count on Jan. 30 showed the presence of 2% segmented neutrophils. A bone-marrow examination demonstrated normal numbers of all cell elements except for an increase in reticuloendothelial cells and monocytes. There was a relative decrease in cells of the myeloid series. Because of the degree of monocytosis, some consideration was given to the possibility of monocytic leukemia. On review of the bone marrow and the peripheral blood specimens, it was considered more likely that monocytosis represented a compensatory increase due to the absence of neutrophils in the response to infection.

A study of the patient's and mother's blood protein revealed the child's total protein as 6 gm. % with a gamma-globulin of 1.4 gm. %. The mother's total protein at this time was 9.6 gm. % with a markedly elevated gamma-globulin of 3 gm. %. Employing the method of Dausset,[26] we were unable to demonstrate any agglutination of normal neutrophils by using the infant's serum.

In spite of repeated transfusions, antibiotics (dihydrostreptomycin), oxygen, and other supportive therapy, the cellulitis of the nose, cheeks, and lips became more extensive and gangrenous. A similar lesion appeared on the skin of the perianal area. The child died on Jan. 31, 1955—the 6th hospital day.

Necropsy Findings
(Dr. A. C. Aufderheide)

Necrotic, ulcerated areas were present on the face and anal region. The heart appeared normal. Except for irregular consolidation of the right

upper lobe, the lungs were not abnormal. A superficial ulcer measuring 3 cm. in diameter was found in the terminal ileum. The liver weighed 190 gm. and was without gross change. The spleen weighed 18 gm. and was dark blue-red. There was no enlargement of lymphoid structures. The urinary, genital, skeletal, and muscular systems were without gross change. The brain showed brownish discoloration of the meninges over the ventral surface of the left frontal lobe but no internal gross pathology.

Histologic findings: The right upper lobe of the lung showed the presence of mononuclear cells in the alveoli. The ileal ulcer was surrounded by nonspecific inflammatory changes, and bacterial stains showed the presence of both rod and coccal forms. Occasional neutrophils were found in the spleen, and small areas of extramedullary hematopoietic tissue occurred in the liver. All lymph nodes examined were benign. Hydropic degeneration was noted in the proximal convoluted renal tubules. The brain revealed the presence of acute purulent meningitis without demonstration of organisms. The bone marrow was solidly cellular with evidence of participation by all elements, including erythroid, myeloid, and megakaryocytic cells. Monocytoid cells were present but not predominant. The myeloid series was largely represented by cells in the myelocyte stage, and some progression to mature neutrophiles was seen.

Comments

There is little doubt that our first two patients are examples of cyclic neutropenia. Both patients have been observed for over 10 years and have experienced periodic depression of neutrophils at approximately 21-day intervals. The first patient (Case 1) has been treated conservatively with precyclic administration of antibiotics with fair success. The second patient (Case 2) has had splenectomy with reduction of symptomatology. This patient still requires frequent use of antibiotics to keep her infections under control.

The cause of the agranulocytosis in the infant remains open to question. Many cases of cyclic neutropenia have onset in early infancy, and in one other instance familial occurrence has been reported.[27] We could not conclude that a drug idiosyncrasy would explain this child's illness, and there was no suggestion of aplastic anemia in the bone marrow. The Coombs test was negative, and agglutinations for antileukocytic antibodies were absent, thus ruling out congenital neutropenia.

It is our impression that this child had cyclic neutropenia because of the early return of neutrophils in the peripheral blood the day prior to death. Also, bone marrow aspiration on admission showed a decrease in the myeloid cells, while the postmortem examination showed them to be present in normal amounts with progression into neutrophils. These changes are similar to those described by Page and Good as "maturation arrest."

The death of this infant again demonstrates the high mortality among children[34] and debilitated persons with gangrenous pyoderma and septicemia caused by Pseudomonas organisms. The prognosis is even more grave when in association with granulopenia, as in this child.

We have been interested in the findings of Page and Good on the response of skin to trauma during a neutropenic phase. The lack of characteristic inflammatory change following injury appears unique. Their studies would indicate that localized trauma might be very important in the production of cutaneous lesions in these patients. The frequency of their infections occurring in areas of friction, namely, axillae, groins, and buttocks, as well as in the mouth, would point to trauma as a significant factor in the development of these eruptions during the periods of neutropenia.

Summary

Recurrent aphthous ulcers, gingivitis, and cutaneous infections (especially occurring in the axillae, groins, and gluteal area), appearing at regular intervals, should stimulate the clinician to consider the unusual hematologic disorder, cyclic neutropenia. In this disease, the total white blood cell count is always in the low-normal range, and the neutrophils drop to low levels at regular periods averaging 21 days.

Thirty-three cases of cyclic neutropenia reported in the literature have been reviewed. Experimental work directed at elucidating the etiology of the disease has

been discussed. Patients show clinical improvement upon administration of steroids, but no alteration of their cyclic blood changes occurs. Splenectomy is of some therapeutic value if the patient is over 25 years of age and has splenomegaly. In most instances, the use of antibiotics, when the infections are severe, aids in recovery.

We have described the course of the disease in three patients, two of whom have been observed for a period of over 10 years. The third patient, the infant daughter of one of these, died at seven weeks of age with sepsis, gangrenous pyoderma, and granulocytopenia. Autopsy and laboratory studies are reported.

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ABSTRACT OF DISCUSSION

DR. WILLIAM N. PIPER JR., Los Angeles: Dr. Becker has reported three additional cases of an unusual and interesting hematological disorder. In addition, he has again indirectly reemphasized the importance of the dermatologist as an internist specializing in the cutaneous features of internal disease.

There are many cycle phenomena found in man, and, in general, these may be classified as either physiological or pathological. In the former group, we observe, in part:

1. The normal menstrual cycle with its cellular, chemical, and fluid changes
2. The diurnal rhythm of eosinophilia, body temperature, salt excretion, and mitotic activity
3. There are many other cyclic phases dependent upon the environmental or metabolic stimuli

In the latter group, pathological examples may include:

1. Periodic disease
2. Cyclic thrombocytopenia
3. Armenian disease
4. Periodic familial paralysis
5. Malaria
6. Pel-Epstein fever
7. Cyclic neutropenia

To entertain and confirm the diagnosis of cyclic neutropenia, the clinician must consider other entities, including the leukopenias, of various types and this subject has been extensively covered by Dr. John Lawrence in the *Journal of Chronic Diseases*, 1957; pyodermas, as impetigo and pyoderma gangrenosa; the vesiculo-bullous dermatoses, and ulcerative entities of the mucous membranes, such as aphthous ulcers.

It is opportune, however, that the clinical symptoms appear in cyclic neutropenia approximately three days prior to the peripheral neutropenia. Thus, the clinician has adequate opportunity to evaluate the blood findings. Subsequent bone marrow examinations will confirm the blood pathology.

As Dr. Becker has suggested, this disease offers us a laboratory in which we might clinically approach such problems as the role of leukocytes and lymphocytes in inflammation and infection, eosinophilia, and such bizarre dermatoses as aphthous ulcers, dermatitis herpetiformis, and the leukemid eruptions.

His presentation has also illustrated the fact that once an unusual entity is reported, the physician's index of suspicion is stimulated, and additional cases are found.

In conclusion, I would like to ask Dr. Becker if serial hematological studies have been either effected or reported in other dermatoses with similar cutaneous manifestations. I should also like to thank Dr. Becker both for his excellent presentation and for the stimulating thoughts he has offered.

DR. STEPHEN ROTHMAN, Chicago: I should like to inquire on the genetics of this condition. Is it generally accepted that this is a familial disease, and, if so, of what type? Practically, it would be important to advise patients not to have children if this is a Mendelian dominant trait.

DR. FREDERIC T. BECKER, Duluth, Minn.: As far as I know, serial white counts have not been done on other dermatological entities.

In answer to Dr. Rothman, in the review of the literature,[27] we could find only one other report of a familial incident. We have studied this patient's family and found no others involved and have also examined the patient's two other children who at this time appear to be normal. I think this is an important disease for dermatologists because I originally saw both of these patients and I was not aware of the proper diagnosis. They were faithful enough to come back to see me at periodic intervals until I became enlightened as to this entity. I am sure other dermatologists will sometime see patients with this diagnostic problem.

Pustular Patch Test Reactions

With Particular Reference to Those Produced by Ammonium Fluoride

ALEXANDER A. FISHER, M.D.; LOUIS CHARGIN, M.D.; RAUL FLEISCHMAJER, M.D., and ARTHUR HYMAN, M.D., New York

In sensitized persons, patch tests with allergens may show a local reaction varying from a mild erythema to erythema with edema, papules, and vesicles. Such reactions are usually graded 1 to 4 plus depending upon the degree of reaction. Patch tests with many primary irritants may show somewhat similar local reactions. In some instances, however, the reactions are so severe as to produce ulcerations. These two commonly observed reaction types, however, do not appear to cover all forms of reactions that occur from patch tests.

There exists still another type of patch test reaction which differs in many respects from the above mentioned. Sulzberger and Witten have called attention to a pustular type reaction which, it appears, has escaped general notice, and consequently has not had adequate work-up. These pustular patch test reactions are especially produced by certain salts of heavy metals and halogens. Usually, the pustules are small, measuring 1-2 mm. in diameter. However, patch tests with 2% aqueous solution of ammonium fluoride often produce much larger, bizarre-looking, milky pustules which differ to an extent from the more commonly produced small pustules just mentioned.

The purpose of this study is to determine the nature of the two types of pustules and to differentiate them from primary irritant and from allergic eczematous reactions. In addition, certain unusual features of pustular reactions to ammonium fluoride will be emphasized.

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From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Skin and Cancer Unit of the New York University Hospital.

Procedure

A study was made of patch tests with the following materials:

1. Ammonium fluoride (2% aqueous)
2. Potassium iodide (30% in petrolatum)
3. Nickel sulphate (10% aqueous)
4. Sodium arsenate (10% aqueous)

These substances were chosen because they produced the vast majority of pustular reactions.

Histologic, bacteriologic, and cytologic examinations were made of eight pustules produced by patch testing with ammonium fluoride and of five pustules resulting from patch testing with each of the other substances mentioned above. The testing was done at various seasons of the year in an attempt to obviate changes due to heat, cold, excessive sweating, or dryness. There were twenty atopic persons in this study. Otherwise, there was no selection of patients. A total of 1,459 persons were tested.

Results

Table 1 shows the number of patients who were given patch tests with the substances mentioned and the number and percentage that showed allergic eczematous reactions or pustular reactions.

It had previously been observed that the interior of glass bottles in which 2% aqueous ammonium fluoride had been stored for more than one month showed an etching effect upon the glass from this chemical. It was, therefore, decided to compare the results of testing with ammonium fluoride stored in bottles coated with paraffin (paraffin alone tested on 20 persons gave no reaction), and the same solution stored in uncoated bottles. Table 1 shows that 8.1%

TABLE 1.—*Results of Patch Testing with Halogens and Certain Heavy Metal Salts*

Substance	No. Cases Tested	Allergic Eczematous Reactions	% Allergic Eczematous Reactions	Pustular Reaction	% Pustular Reaction
Ammon. fluoride, uncoated bottle	241	1	0.4	22	8.1
Ammon. fluoride, paraffin-coated bottle	186	1	0.5	27	14
Paraffin alone	20	0	0	0	0
Nickel sulfate	687	34	5	9	1.3
Sodium arsenate	240	2	0.8	19	6
Potassium iodide	85	1	1.2	4	4.5

of patients tested with ammonium fluoride from uncoated bottles reacted with pustular reactions, whereas, 14% of patients similarly reacted to ammonium fluoride stored in paraffin-coated bottles. Ammonium fluoride produced very few allergic eczematous reactions whether the agent was stored in uncoated or coated bottles. The actual figures were 0.4% and 0.5% allergic eczematous reactions, respectively.

Nickel sulphate, which produced the largest number of allergic eczematous reactions (5%), produced the smallest number of pustular reactions (1.3%).

Sodium arsenate, on the other hand, produced 0.5% allergic eczematous reactions

TABLE 2.—*Analysis of Pustules Produced by Ammonium Fluoride*

	No. Persons Reacting with Pustules	Small and/or Large Pustules	Large Pustules Only
Uncoated bottle	22	19	3
Paraffin-coated bottle	27	22	5

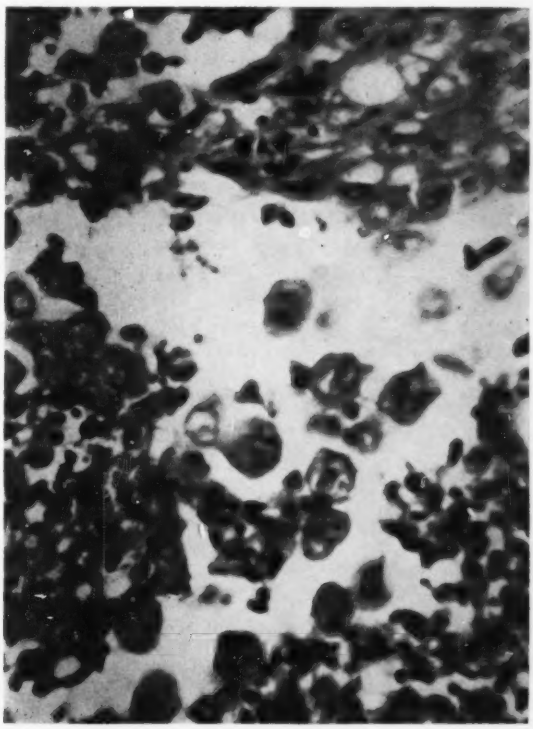

Fig. 1.—Showing features of acantholysis.

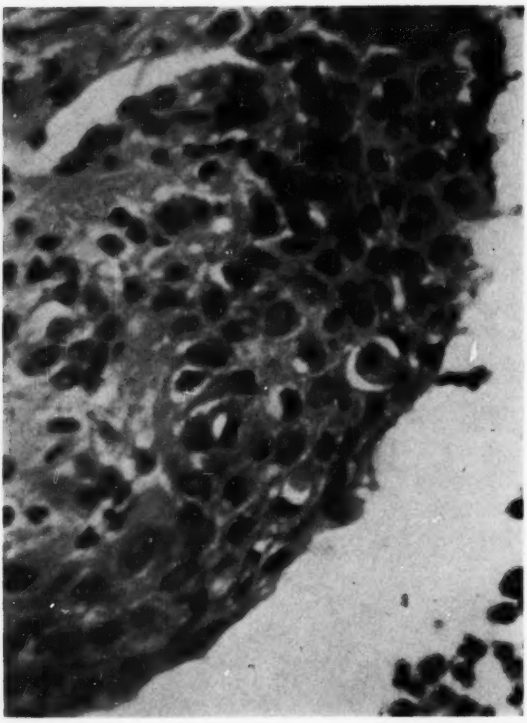

Fig. 2.—Showing features of balloon degeneration.

and 6% pustular reactions, while potassium iodide produced 1.2% allergic eczematous reactions and 4.5% of the pustular variety.

Table 2 reveals that in 49 tests ammonium fluoride produced pustular reactions. The ammonium fluoride from the uncoated bottle produced large pustules exclusively in (3 of 22) 14% of the patients, while the fluoride from the paraffin-coated bottle produced large pustules exclusively in (5 of 22) 19%. In the remainder of the persons tested the fluoride from either bottle produced a mixture of small and large pustules.

Figure 1 shows the most common type of pustular reaction produced by ammonium fluoride consisting of a single large pustule 4 mm. in diameter, surrounded by several small pustules. Both the large pustules and the smaller ones show some degree of umbilication, somewhat resembling herpetic lesions.

Figure 2 shows large bizarre pustules which ammonium fluoride produced in 8 patients. Most of these pustules were multiple and varied in size from 5 to 9 mm. There was central umbilication or a superficial necrosis of all the large pustules. There was very little clinical evidence of inflammation in the surrounding skin. The patients did not complain of itching or burning in the areas of the large pustules. All the pustules healed without evident

TABLE 3.—*Results of Retesting with Ammonium Fluoride in Eight Persons in Whom Large Pustules Were Originally Observed*

	Production of Original Pustules	Pustules Reproduced	Failure to Reproduce Pustules
1	Aug. 1957		April 1958
2	June 1958	July 1958	
3	Aug. 1957		Sept. 1957
4	May 1958		June 1958
5	Sept. 1957		Oct. 1957
			May 1958
6	Aug. 1957		Oct. 1957
7	Aug. 1957	April 1958	
8	June 1957	Aug. 1957	May 1958

clinical scarring. This type of reaction occurred in five women and three men.

In contrast, the pustules produced by nickel sulphate, sodium arsenate, and potassium iodide were small in size (1-2 mm.). Occasionally, only a single pustule was seen under the patch. Frequently, however, three and four pustules resulted from the patch test with these substances.

Although a study of Table 3 seems to indicate that the large pustules were produced mostly in the warmer months of the year, we have recently observed that such pustules can appear at any time of the year. A feature that should be stressed is that the pustules *cannot be regularly reproduced.* In only three of the eight persons studied could we reproduce this type of pustular reaction on retesting at a later date.

Occasionally, patients showed pustular reactions to more than one of the substances tested as follows:

1. Nine persons reacted with pustules to both ammonium fluoride and the sodium arsenate.

2. Two persons showed pustular reactions to potassium iodide and sodium arsenate.

3. Two cases showed pustular reaction to three substances. One reacted to potassium iodide, sodium arsenate, and ammonium fluoride, and the other to ammonium fluoride, nickel sulfate, and sodium arsenate.

4. One person showed pustular reactions to both nickel sulfate and potassium iodide.

There were twenty atopic persons in this series; only 5 reacted to the patch tests. It is worthy of note that none reacted with large pustules to ammonium fluoride. Two reacted with small pustules to ammonium fluoride, and two to nickel sulfate. One atopic person showed a pustular reaction to sodium arsenate. None of the patients with atopic dermatitis reacted to more than one substance.

The Results of Histopathologic Studies

1. *The Character of the Pustule Produced by Ammonium Fluoride.*—Histologic examination of the smaller type pustules showed it to be essentially a vesicle and contained a preponderance of lymphocytes as against polymorphonuclear cells. Some of the pustules were mushroom shaped with the base penetrating the upper cutis. The lateral walls of the pustules were separated by clefts from the epidermis. Older pustules invaded to the midcutis. Surrounding the vesicle there was an infiltrate mainly of small round cells with a few polymorphonuclear cells. No spongiosis was seen. The superficial vessels were dilated and there was some edema of the upper cutis. Around the vessels there was a focal infiltrate of lymphocytes, histiocytes, and some polymorphonuclear cells.

In the larger pustules produced by ammonium fluoride, the surface was denuded of epidermis. Under the erosion, in the cutis, there was a massive infiltrate composed of lymphocytic and pyknotic elements with considerable cellular debris and some polymorphonuclear cells. To either side of the denuded area where epidermis was still visible, the epidermal cells showed poor staining. These cells had become more or less rounded to produce the features of acantholysis. In addition, many cells in the epidermis showed rather marked *intracellular* edema. These cells had become large and round, and the cytoplasm pale staining to simulate the changes seen in *"ballooning degeneration."* In addition, there were the changes of reticular degeneration in this area of the epidermis. No spongiosis was noted.

The large pustules invaded the upper and middle cutis. The cutis showed a pronounced massive infiltrate composed mainly of small round cells, some polymorphonuclear cells, a few eosinophils, and red blood cells. There was considerable cellular destruction in both the pustule and the cutis infiltrate with much cellular debris and pyknotic elements in evidence.

The finding of "ballooning degeneration" suggested the possibility of the presence of a virus or other inclusion bodies.

Three slides were stained with Feulgen, McManus, and Giemsa stains. However, examination of the slides with these special stains revealed no findings of further value to the study.

2. Pustules Produced by Nickel Sulfate, Sodium Arsenate, and Potassium Iodide.—These pustules tended to resemble those produced by ammonium fluoride except that (*A*) there was present a relatively greater number of polymorphonuclear cells in the pustule and in the dermal infiltrate as compared with ammonium fluoride; (*B*) there was no evidence of "ballooning degeneration" in the cells of the epidermis, which was an outstanding feature in the large pustules produced by ammonium fluoride; (*C*) there was a greater tendency for aggregation of polymorphonuclear and small round cells about the follicles with these three substances, and (*D*) mild spongiosis could occasionally be seen with pustules produced by nickel sulfate, etc., but usually not with those produced by ammonium fluoride.

Results of Bacteriologic Examination

Smears of the fluid content of the pustules from ammonium fluoride showed no bacteria on direct examination. Staining of the fluid content of the pustules for bacteria did not reveal any organisms. On culture various strains of staphylococcus, streptococcus, and enterococcus were isolated. In five cases these organisms were coagulase negative, (nonpathogenic); one case showed colonies of Staphylococcus pyogens var. albus, coagulase and mannite negative; and Staphylococcus pyogenes var. aureus, coagulase and mannite positive. These organisms were considered either nonpathogenic or secondary invaders but *not direct producers* of the pustules.

Results of Cytologic Examination

Fluid obtained from 4 large pustules produced by ammonium fluoride were examined after processing with Wright's stain. Lymphocytes and monocytes were grouped together as mononuclear cells. At least 100 cells were counted in each smear. Table 5 reveals that, while there were more polymorphonuclear cells than mononuclear cells, the preponderance of polymorphonuclear cells was not as great as is usually seen in the vesicles produced by ordinary primary irritants.

TABLE 4.—*Results of Cytologic Examination of Fluid Obtained from Ammonium Fluoride Pustules*

	Polymorphonuclear Cells	Mononuclear Cells
1	70%	30%
2	56%	46%
3	65%	35%
4	63%	37%

Comment

Clinical Features of Pustular Patch Test Reactions.—The clinical features which seem to distinguish pustular patch test reactions produced by the halogens and heavy metal salts from allergic eczematous and ordinary primary irritant patch test reactions are as follows:

1. Pustular patch test reactions are symptomless, while allergic eczematous patch test reactions often itch. The usual primary irritant patch test reaction may cause both itching and burning.

2. Pustular patch test reactions cannot be regularly reproduced and occur in a minority of patients. Allergic eczematous patch test reactions usually can be regularly reproduced once the patient has become sensitized. The ordinary primary irritant patch test reactions occur in the majority of persons and usually can be regularly reproduced.

3. Pustular patch test reactions heal promptly after the patch is removed usually in 24 hours. Allergic eczematous patch test reactions may be evident for several days to weeks and may even increase in intensity after the removal of the patch. Patch test reactions due to primary irritants may occasionally be so severe that they may persist for several days or longer and cause scar-

ring. Clinical scarring has not been observed with pustular reactions due to the metal salts or the halogens.

General Histopathologic Considerations of Allergic and Primary Irritant Patch Test Reactions

Braun [1] studied the cellular infiltrate in allergic eczemas and found a preponderance of lymphocytes as against polymorphonuclear cells. He further noted that in very intense allergic reactions, polymorphonuclear cells may predominate.

Nexmand [2] made differential counts with Giemsa stain on vesicular and bullous eczematous reactions and on reactions due to primary irritants. This study revealed that mononuclears are predominant in the allergic reactions, whereas polymorphonuclears are the predominant cells in primary irritant reactions. Baer and Yanowitz [3] confirmed and extended these findings and showed that there are differences in the cellular content of blister fluids produced by different primary irritant vesicant agents.

Baer and Witten [4] summarized the distinguishing features of allergic eczematous eruptions as follows:

1. In the epidermis—intercellular edema (spongiosis) and vesicle formation usually starting in the lower part of the prickle cell layer.

2. In the dermis—edema and perivascular cellular infiltration, predominantly with mononuclear cells.

3. In the vesicle fluid—a considerable number of mononuclear cells.

These authors further stated that the following changes are more characteristic of a primary irritant eczematous reaction:

1. In the epidermis—intercellular edema (spongiosis) and vesicle formation usually starting near the surface; may show early erosion and necrosis.

2. In the dermis—progression of necrosis; perivascular reaction is variable.

3. In the vesicle fluid—predominance of polymorphonuclear cells.

Histopathologic Features of Pustular Patch Test Reactions

Sulzberger and his co-workers [5,6] have long been interested in the phenomenon of pustular reactions. Sulzberger and Witten [7] commented specifically on the differences between pustular patch test reactions due to the salts of heavy metals and allergic eczematous patch test reactions. These authors have pointed out that, instead of the spongiosis and vesiculation of the stratum mucosum, such as is present in the allergic eczematous reactions, there is more superficial corneal and subcorneal primary irritation with a not inconsiderable leukotaxis in pustular patch test reactions. Furthermore, they noted small areas of superficial "etchings" and polymorphonuclear infiltrates in these pustular patch test reactions.

An analysis of our material also revealed that intercellular edema (spongiosis) was slight or absent in the pustular patch test reactions. This is in contrast to the spongiosis which is usually very prominent in both the allergic eczematous and primary irritant eczematous patch test reactions.

Areas of superficial "etchings" or "erosions," such as Sulzberger and Witten described were seen with all varieties of pustular patch test reactions. This was particularly noted in the large pustules produced by ammonium fluoride. While large pustules were produced in a somewhat greater percentage of persons by ammonium fluoride which had been stored in bottles coated with paraffin to prevent etching on the interior of the glass container, the difference could not be regarded as statistically significant.

"Etchings" or "erosions" can also be caused by ordinary primary irritants, but in such instances usually there is *spongiosis* present. "Etchings" or "erosions" of the epidermis *without spongiosis* would appear to be a feature of pustular patch test reactions. In addition, there was a unique finding noted in the large pustules produced by ammonium fluoride which to our knowledge had not previously been reported. This

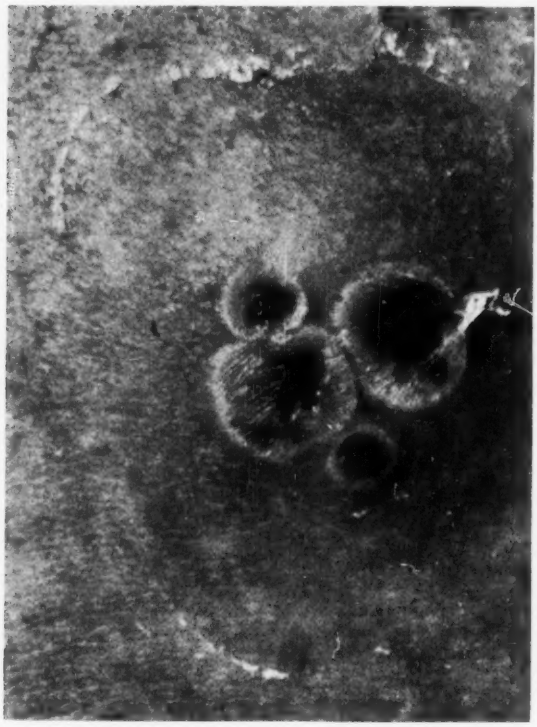

Fig. 3.—Showing large pustules.

feature consisted of the production of a rather marked acantholysis and changes resembling "ballooning degeneration" of epidermal cells. Such changes were not seen in our material in pustular reactions produced by nickel sulfate, sodium arsenate, or potassium iodide. Nor did *small* pustules produced by ammonium fluoride reveal the features of acantholysis nor those simulative "ballooning degeneration."

Examination of the areas of acantholysis and changes resembling "ballooning degeneration" with special stains did not reveal the presence of viruses or other inclusion bodies.

The Cellular Content of the Pustules

Examination of the fluid from the pustules revealed the presence of many polymorphonuclear cells and many mononuclear cells with neither type of cell predominating. The vesicle fluid of allergic eczematous patch test reactions characteristically contains a greater proportion of mononuclear cells, while that of a primary irritant patch test reaction usually shows a predominance of polymorphonuclear cells.[3,4]

Summary and Conclusions

The clinical significance of pustular patch test reactions produced by the halogens and certain salts of heavy metals remains obscure. Such reactions occur in only a *minority* of individuals and are not regularly reproducible. They occur in both atopic and nonatopic persons. These pustules are asymptomatic, sterile, and heal without clinical scarring.

The presence of "etchings" or "erosions" in the epidermis without spongiosis is characteristic.

Ammonium fluoride is unique in producing large pustules which show acantholysis and changes simulating "ballooning

Fig. 4.—Large pustule surrounded by several small pustules, some showing umbilication.

degeneration" in the epidermis. These findings are not present in any other type of patch test reaction we have examined, including the smaller pustules produced by ammonium fluoride, sodium arsenate, nickel sulfate, and potassium iodide.

The cellular content of the pustules consists of many polymorphonuclears and mononuclear cells with neither type distinctly predominating.

In agreement with previous observers, our findings also indicate that pustular patch test reaction due to halogens and heavy metals warrant separating into a special category. They are distinct clinically and histopathologically from both allergic and primary irritant patch test reactions.

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ABSTRACT OF DISCUSSION

DR. STEPHAN EPSTEIN, Marshfield, Wis.: The papular and pustular reactions from heavy metals and other chemicals have been of interest to many of us. But, to my knowledge, nobody so far has

published a systematic study about them. Therefore, Dr. Chargin and his collaborators should be congratulated for providing such an investigation. Theirs has been a fruitful study because they present new observations and pose many new questions.

First of all, where do these reactions belong? Sulzberger always maintained they are toxic reactions. Becker and O'Brien (A.M.A. ARCH. DERMAT. 79:569 [May] 1959) believe that the reactions result from dermal allergy and not from primary irritation, in contrast to Sulzberger. Chargin and his collaborators separate these reactions into a special category. It sounds confusing and it is. I shall add to the confusion. Who is right? I believe all three are right, but I do not believe that Sulzberger, Becker, and Chargin talk about exactly the same phenomena.

Sulzberger referred to those papulopustular reactions seen especially with heavy metals in atopic persons as first described by Steiner. I am convinced that these reactions are a toxic manifestation. In patients presenting this type of reaction, there is no clinical evidence of allergic hypersensitivity to the reacting metal. Furthermore, intradermal tests with metals are negative in this category. Finally, as Dr. Chargin has shown, these tests cannot be reproduced regularly, and that has also been my experience.

Becker and O'Brien described the so-called folliculoporal patch test reactions, which, I believe, are a different entity. These are diffuse follicular reactions which usually can be easily distinguished from the papulopustular metal reactions in atopic persons. These reactions are observed in patients clinically sensitive to the reacting metal, and I believe, with Becker and O'Brien, that they are an expression of dermal sensitivity. Intradermal tests with metals are usually positive in these instances. As Becker has emphasized a long time ago, and as Jielson (*Ann. Allergy* 17:215 [March-April] 1959) has stressed again, they seem to occur often or mainly in atopic persons.

Dr. Chargin's presentation grouped together the papulopustular reactions from metals with the purely pustular reaction from ammonium fluoride. Perhaps, he has unwillingly contributed to the confusion, that he added as an afterthought in his study the papulopustular reactions from heavy metals. I shall restrict myself to these unusual umbilicated vesicles from ammonium fluoride which are unique reactions and occur only with ammonium fluoride. I believe, however, they are a toxic phenomenon or one of primary irritancy, whatever term you prefer. This is also suggested by their effect on glass.

Dr. Chargin's cytologic findings support the view of a primary toxic reaction. I beg to disagree but I think his figures showed a preponderance of polymorphonuclear cells. They amount to 64% in his cases, and that agrees very well with the study of Baer and Yanowitz, who found (*J. Allergy* 23:95 [March] 1952) an average of 76% of polymorphonuclears in the blister fluids from a primary irritant.

It seems to me the main distinction still is between allergic and toxic reactions to patch tests. Both forms of reactions have special groups. In the allergic group, there are epidermal and dermal reactions. The toxic or primary irritant reactions to patch tests show many different forms. Some produce blisters, as cantharides; some a mild dermatitis, as detergents and soap; others, superficial necrosis, as phenol, and so on. Dr. Chargin's pustular reactions with ammonium fluoride apparently form a special group within the toxic reactions. No doubt, further studies may show still more patterns of reactions. I have, for instance, observed on several occasions in atopic persons that patch tests with 10% cobalt nitrate produce petechiae, but I have seen these hemorrhagic reactions only with cobalt nitrate.

Dr. Chargin has given us a very stimulating presentation, and I am sure others will follow suit to explore the nature of these papular and pustular reactions from halogens and heavy metals.

DR. SAMUEL M. PECK, New York: I rise very humbly to acquaint the membership with a unique fact. Here is a gentleman, on the threshold of his eightieth year, who is presenting to us not a historical summary of his opinion of what has been presented, but actual active research work. I should say his brain is more nimble than the melanin function of his hair bulb, since his hair is still dark. I wish to congraulate him for a wonderful paper, which has given me stimulus to continue active research as I approach the threshold of those golden years myself.

In a recent issue of the *Clinics of North America* edited by Dr. Sulzberger ("Contact Dermatitis" *The Medical Clinics of North America,* [May] 1959, p. 831), I attempted to classify primary irritants from the viewpoint of their role in contact dermatitis.

Once you recognize a substance as being a primary irritant, you have a medicolegal responsibility when you do a patch test. Any scarring resulting can be defined perhaps as malpractice.

I divide my primary irritants into three different groups: (1) the strong or obvious, (2) the mild, and (3) the insidious. This last group takes weeks or even months to produce its irritation and usually has a specific mechanism or affects a particular part of the skin or its appendages. I believe that ammonium fluoride falls into the strong or obvious primary irritant. The histologic reaction depends in some part on the chemical nature of the primary irritant. It is obvious that coagulants will give one histologic picture, dehydrators another, and vesicants still another type of histologic response.

The pustular follicular reaction is characteristic for a host of primary irritants, especially the chlorinated hydrocarbons, the cutting oils, the tar acnes, etc.

I do not believe that the action of ammonium fluoride warrants a special classification but falls into the group of the strong irritants, which may have a peculiar action depending on their chemical reaction with the skin.

DR. S. WILLIAM BECKER, Long Beach, Calif.: Dr. Chargin has performed a real service in directing our attention to this interesting type of patch test reaction. In studies I previously made (Becker, S. W.: A New Interpretation of Some So-Called Positive Patch Test, with Special Reference to Metals Used in Industry, *J. Michigan M. Soc.* 44:65-69 [Jan.] 1946), it was concluded that follicular and poral reactions to chrome and nickel signified dermal allergy, and that the dermatitis which persisted after removal from the occupational contact was neurodermatitis rather than epidermal allergic contact dermatitis. This concept was further amplified by serial patch tests (Becker, S. W., and O'Brien, M. P.: Value of Patch Tests in Dermatology, A.M.A. ARCH. DERMAT. 79:569-577 [May] 1959).

A recent patient is illustrative. A 50-year-old male dentist developed dermatitis of the feet, then of the hands, in March, 1958. By June, 1958, it was so severe he had to quit work and, though he had not worked for one year, he still had severe dermatitis of the hands. Patch tests revealed folliculoporal reaction to formaldehyde, nickel, chrome, copper, and fluorides. There were no vesicular reactions of the usual contact type. Examination in the Allergy Clinic revealed positive dermal tests to feathers, dog-hair, and shell fish. He is from an allergic, unstable family. An identical twin and a sister, both formerly asthmatic, now have dermatitis of the hands. Another brother and his mother committed suicide. The dermatitis was interpreted as neurodermatitis, rather than allergic contact dermatitis to substances used in his work.

DR. JOSEPH V. KLAUDER, Philadelphia: I should like to discuss a possible practical application from the studies of Dr. Chargin.

Dr. Chargin has applied a 2% aqueous solution. Dr. Becker has shown that a 5% aqueous solution is apparently safe to apply on the skin. Dr. Chargin has shown that there is little cutaneous reaction. I should like to ask, was there any other reaction? Was there deep-seated pain? The fluoride compounds are extremely active. They have a wide use in industry. Industrial chemists call them a devil that has been chained. Hydrofluoric acid burn is an occupational dermatosis; severe pain is a characteristic feature (Klauder, J. V.; Shelanski, M. A., and Gabriel, K.: Industrial Uses of Compounds of Fluorine and Oxalic Acid, A.M.A. ARCH. INDUST. HEALTH 12:412 [Oct.] 1955). Solution of oxalic acid in contact with the skin causes little objective cutaneous reaction but severe pain that is sleep disturbing. In both instances the severe pain is reasonably attributed to disturbance of the calcium potassium ratio in the skin resulting in nerve stimulation by potassium. Administration of calcium is effective in relieving pain.

An aqueous solution of oxalic acid is apparently absorbed through the skin. Pain after cutaneous contact with an aqueous solution of ammonium fluoride would suggest absorbtion. Hence my question regarding pain.

My thought is, could ammonium fluoride be used in the treatment of silica in the skin, which is a difficult substance to remove from the skin? Could it be used in the treatment of a silica granuloma? Could it be used too, perhaps, in a fraction of a per cent in washing a newly inflicted wound, in which there is a possibility of silica being imbedded in the skin? Many fluoride compounds are chemically active and fix silica. Such compounds are used in the etching of glass and in the cleaning of marble.

There is another consideration, in view of this chemical activity. If one fails, as observed by Dr. Chargin, to reproduce a cutaneous reaction which had been previously produced, in explanation consideration should be given, as to what is on the surface of the skin at the time ammonium fluoride is applied. I refer to a variety of substances that may counteract the action of fluoride, and thereby cause a failure of the cutaneous reaction.

DR. A. ROSTENBERG JR., Chicago: I, too, enjoyed the paper by Dr. Chargin and his associates, and, as Dr. Chargin was one of my early teachers in dermatology, it is with some reluctance that I align myself on the side of those who disagree mildly with his interpretations.

It seems to me, in attempting to evaluate the nature of patch-test reactions, one comes pretty soon to a dead end if one attempts to classify these on more or less morphological characteristics, be they gross or microscopic. We have to probe a bit deeper, as we do in most other situations, and ultimately get down to what is the mechanism by which the reactions are produced.

In general, I should think that all cutaneous reactions are produced by some biochemical alteration, presumably an interference with some enzyme system. However, one can subdivide this into two large categories, one in which the enzymatic interference presumably comes about by way of an antibody mechanism—and I shall not try to define precisely what we mean by an antibody mechanism. This is, of course, the allergic type of reaction and, in this case, we usually add the label, "eczematous type of allergic reaction." But it requires the necessary intermediation of the antibody mechanism, which, of course, in turn, requires certain prior sequences of events.

The other types of reactions which interfere with enzyme mechanisms may do so directly, and these, I think, should be classed under the general label of primary irritant mechanisms. Of course, there will be somewhat of a diversity of appearance in these, by virtue of the enzyme system that is affected.

In my review, which I wrote a few years ago, on comparisons between allergic eczematous reactions and primary irritant reactions, I pointed out that in the allergic eczematous reaction the chief variable was the host, whereas in the primary irritant reaction the chief variable is the material itself. It is well-known that fluorides are sulfhydryl inhibitors, that is, enzyme systems that depend on some sort of sulfhydryl grouping are, by and large, knocked out by fluoride; hence I do not think it at all surprising that the fluorides should produce a lesion such as Dr. Chargin has shown us.

However, most of us, myself included, were not aware of the intensity of the response that could be developed.

One other comment is concerning the concept of dermal allergy. This is not one that Dr. Chargin brought out in his paper, but several of the discussers have used the term or have talked of such a state. I must confess I do not know of any such state. I know of no evidence to divide delayed type reactions into epidermal cutaneous allergy and dermal cutaneous allergy.

In conclusion, then, I think that it is more useful to classify a patch test or other types of cutaneous reactions according to the mechanism. In one case it requires the intervention of an antibody, and in the other cases it does not require it. I should like to thank Dr. Chargin and his collaborators for drawing our attention to this morphological response.

Dr. Louis H. Winer, Beverly Hills, Calif.: As Dr. Rostenberg indicated, this is a different type of pathologic reaction than was shown by Dr. Becker. Dr. Becker showed vesicles and pustules developing as a result of alteration *cavitaire* of Leloir; a liquefaction degeneration of cellular cytoplasm of the epidermal cells, secondary to the vascular changes.

Dr. Chargin, on the other hand, showed the fracturing of the sulfhydryl bonds, a breaking down of the prickles between the cells, as was shown by Dr. Staughton in an exhibit at the Academy of Dermatology two years ago. Apparently the chemical here also dissolved away the sulfhydryl, or other bonds, and created acantholytic cells in the epidermal rete.

Dr. Louis Chargin, New York: Dr. Epstein has somewhat widened the discussion beyond the scope of our presentation and has brought up interesting points worthy of consideration. In connection with our presentation, however, the findings with the group of agents we employed presents evidence that patch test reactions differ markedly from those seen in allergic eczematous or primary irritant reactions in several respects, namely, in clinical aspect, in the pathologic findings, and in cytology. Whether we are dealing with reactions that are allergic or primary in nature, frankly, we were unable to decide. Dr. Epstein points to the somewhat greater polymorphonuclear count as against the uninucleated in the ammonium fluoride pustule. The preponderance is, however, small and not like the high count associated with primary reactions, nor is the uninucleated cell count as high as seen in allergic eczematous blister fluid.

Dr. Peck's remarks, always stimulating, are not exactly germane to the subject matter of our discussion. They merit serious consideration and should be followed up.

Dr. Becker's slides certainly point to the difference between the pathology of allergic eczema and those we presented.

Dr. Klauder refers to pain associated with some patch test reactions which as is known, is especially seen in primary reactions. Although the clinical aspect of the ammonium fluoride pustule suggests a deep involvement, in fact, the lesion is superficial and causes only a denudation of upper layers of skin, heals rapidly, and is painless.

Dr. Winer's remarks apropos the pathology is just to the point. In the allergic and primary reactions there is no acantholysis or ballooning degeneration which is so characteristic of the ammonium fluoride pathologic findings.

To Dr. Rostenberg's remarks I can only state it may be that we are not justified in suggesting an additional classification to patch test reactions, but, surely, the clinical pathologic findings we are presenting are not those of allergic eczematous or primary reactions.

Melanotic Freckle

Lentigo Maligna

MAURICE J. COSTELLO, M.D.; STUART B. FISHER, M.D., and CHARLES P. DeFEO, M.D., New York

Melanotic freckle is a pigmented, precancerous lesion that is clinically distinctive, sometimes difficult to interpret histopathologically, and which presents a problem in histological diagnosis, prognosis, and in treatment. It progresses slowly, sometimes to a malignant tumor stage (superficial melanocarcinoma) which may be indistinguishable from malignant melanoma, and yet its prognosis as to metastasis, morbidity, and mortality is comparatively favorable.

Dermatologic literature contains several comprehensive reports of this unusual entity since its original description by Hutchinson.[1] Noteworthy are those of Dubreuilh,[2,3] Meischer,[4,5] Justitz,[6] and more recently, Klauder and Beerman.[7] There have been two hundred cases reported in all. The purpose of this presentation is to record twelve additional cases seen in private practice and clinic practice.

Nomenclature

Melanotic freckle has been described under many names, such as senile freckle, infective melanotic freckle, melanose circonscrite precancereuse, lentigo malin des vieillards, and lentigo maligna. Since the lesion will become more malignant in a statistically significant number of cases, it is classified as a precancerosis.

Incidence

Melanotic freckle is a relatively uncommon lesion. However, not every case observed has been reported, nor has every melanotic freckle been recognized as a separate entity distinct from malignant melanoma. It occurs about equally in males and females. It becomes manifest most frequently in the sixth and seventh decades of life, although it has been noted earlier. It may be present as long as fifty years.

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From Lenox Hill Hospital, St. Clare's Hospital, and private practice.

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Clinical Features

Location.—Seventy per cent of the cases reported have involved the face. The malar eminences predominate, with eyelids and conjunctivas coming next. Involvement of lips, axillae, breasts, fingers, penis, and leg has been reported, and this, together with the occurrence of lesions over the scapula, the deltoid region of the upper arm, and on the foot, in the cases to be described, denotes that any area of the body can be affected. We have under our care at present a patient with extensive involvement of the palate.

Morphology

The characteristics of melanotic freckle are very distinctive and serve to differentiate the entity from malignant melanoma.

There are two recognizable stages of melanotic freckle. The initial precancerous macule appears as a small tan, sepia, or dark brown spot which in the course of years extends peripherally and irregularly. Because of its slow rate of growth, many years may elapse before medical attention is sought. With progression, a play of colors (tan, dark brown, mahogany, gray, and jet black) and areas of concentration of pigment are seen, giving a mottled appearance. The amount and concentration of pigment is not indicative of the degree of anaplasia. It has not been our experience that, as the

lesion extends, areas that were hyperpigmented may become hypopigmented or revert to the normal color of the skin. Transillumination may show many fine, thread-like strands of hyperpigmentation in varying degree intertwined throughout and occasionally extending beyond the clinically apparent borders of the lesion, which suggests the necessity for adequate removal of the lesion.

Conversion to the possible malignant tumor phase is usually denoted by the development of a solitary indurated area within the hyperpigmented macule, although multiple areas of this nature have been noted in our patients. The tumor may progress from a papule to a nodule or even to a cutaneous horn. It may show areas of hyperpigmentation or hypopigmentation, and it may be eroded, crusted, or bleed easily when traumatized. Regional or systemic lymph node metastases are infrequently found at the onset of the tumor stage or even later.

To be considered in the differential diagnosis are lentigo, pigmented basal-cell epithelioma, junction nevus, senile keratosis, ephelis, the melanoplakia, and seborrheic keratosis. When on the mucous membranes, Jaeger-Puetz disease is to be considered.

Histopathology

The histopathologic interpretation depends upon the area and age of the portion of the lesion chosen for biopsy. This accounts not only for the varying interpretations recorded in the literature but also for the lack of unanimity regarding the origin of the primary lesion. It is not our purpose to belabor the various theories regarding the pathogenesis of pigmented lesions. Long-range observation and investigation are needed before they can be properly classified as to pathogenesis, biologic activity, behavior proclivity, prognosis, and proper therapeutic approach.

In our 12 cases observed over a period of 1 to 10 years, the basic histopathologic picture consistently seen is that of a junction nevus. However, features in certain areas suggest that it is a junction nevus of the premalignant type described by Allen and Spitz [8] and Lever,[9] and it is therefore difficult to differentiate these lesions histopathologically from early malignant melanoma.

In heavily cornified areas, lacunae filled with nevus cells containing melanin are found in the stratum corneum. Stout [10] uses this as a criterion of malignancy when he states:

> A mole must be regarded as a malignant tumor capable of metastasis if, one, the melanoblasts have grown through the epidermis as single units or in small groups, so that they can be found in a viable state with stainable nuclei in the overlying keratinized layer; or two, if all or part of the tumor cells are anaplastic and show mitoses. Often both of these criteria are present.

The disorganization of the lower part of the epidermis and its junction with the cutis is made less definite by aggregates of vacuolated nevus cells containing melanin. The papillary bodies are encroached upon and frequently obliterated by clusters of nevus cells from adjacent rete ridges thus producing a somewhat flat dermoepidermal junction. Mitotic figures are rarely seen. Melanophores present in the cutis in considerable numbers are not as dense beneath the dermoepidermal junction as they are at the junction of the middle and upper thirds of the cutis. Occasionally, there is a dense inflammatory infiltrate of the upper part of the cutis, both directly beneath, and at the periphery of the lesion.

It is not unusual to see individual nevus cells or small clusters of two or more nevus cells in the upper part of the cutis beneath its junction with the epidermis, especially in areas of considerable junctional activity. These junction nevus cells are not intimately associated with the rete ridges when sections are serially examined. Invasion of the cutis by junction nevus cells, according to Allen,[11] in the diagnosis of "borderline" melanocarcinomas which he prefers to call "superficial melanocarcinomas," is the essential feature determining whether a lesion is an active junction nevus or an early malignant melanoma. He further states,

"The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must, when juvenile melanomas are excluded, depend on this single fact: *THE PRESENCE OR ABSENCE OF DERMAL INVASION.* It is to be stressed, however, that awesomely little evidence is required for the diagnosis of melanocarcinoma as opposed to junctional nevus."

The histopathologic picture in other areas of a lesion may show deposits of pigment in the basal zone without junction theques; simply aggregates of melanophores in the upper part of the cutis with absent to minimal inflammatory infiltrate; or a pure lentiginous lesion showing elongated and club-shaped rete ridges with hyperpigmentation and an increase in melanocytes of the basal layer.

Treatment

The morphology of the lesion determines the treatment.

Surgical excision is recommended for those melanotic freckles whose extent is reasonable and when the normal anatomy will not be compromised by the procedure. A margin of one-quarter to one-half inch of normal skin should be included in the excision.

Electrodesiccation and curettage of the lesion and an adequate margin of normal skin are especially well suited to large and extensive lesions, especially those located on the face. This procedure provides the patient with an excellent cosmetic, therapeutic, and functional result. It is necessary to treat an ample margin of normal surrounding skin to prevent an extension of the lesion at the periphery of the previously treated area.

In one patient (Case 1 [Figs. 1 and 2]) no attempt was made to eliminate the extensive pigmented portion of the lesion. A cutaneous horn which developed was treated by electrodesiccation and curettage. Conventional superficial roentgen rays were administered to indurated, elevated, hyperkeratotic local areas which developed during the progression of the melanotic freckle.

Prognosis

It has been estimated[3] that one-third of all melanotic freckles, if allowed to progress untreated, will eventually reach the tumor stage clinically, with a concomitant histologic picture of malignant melanoma. In our present era of preventive medicine, it is doubtful that these statistics will be corroborated. Heretofore, however, months and years have transpired before a melanotic freckle underwent malignant degeneration. The range of time in cases herein reported has been 21 months to 30 years. In view of this fact, the age group usually encount-

Fig. 1 (Case 1).—Nov. 15, 1951.

Fig. 2 (Case 1).—March 24, 1955. Induration and keratotic change above and lateral to left ala nasi.

ered, the infrequent metastases, and the rarity of death from metatastic spread, it appears that the life expectancy of a patient with melanotic freckle will not be appreciably shortened.

Report of Cases

CASE 1.—(Figs. 1, 2, and 3).—An 83-year-old white housewife was first seen in private practice on Nov. 15, 1951. On the right cheek was an oval lesion of nine years' duration, measuring 5 cm. by 4 cm., with variegated hues of sepia to jet black. In the center was a nonpigmented cutaneous horn 2.5 cm. long arising from an indurated and eroded base. The pigmented lesion had progressively enlarged over a period of nine years and the cutaneous horn had been present for one year. There was no regional lymphadenopathy or clinical evidence of distant metastases. Clinically, the diagnosis was melanotic freckle with malignant melanoma. A biopsy was performed on the lesion (Biopsy 1), and the cutaneous horn was treated with electrodesiccation and curettage. A roentgenogram of the chest at that time revealed "four fairly well circumscribed, round and ovoid densities in the midportion of the right lung field. These have the characteristic appearance of parenchymal nodules and are entirely consistent with metastases. Impression: Parenchymal metastases, right lung."

When seen on Oct. 25, 1953, the patient had developed a new keratotic lesion on which a biopsy was performed; treatment was by cautery and curettage. A roentgenogram of the chest was reported as follows: "Impression: Parenchymal metastases, right lung, with a slight decrease in size since the previous examination."

Figure 1 was taken in 1951. Figure 2 was taken on March 24, 1955. The pigmented portion of the lesion had increased to 7 cm. by 4 cm., with induration and keratotic change.

From Nov. 25, 1956, to Feb. 9, 1957, a total air dose of 2,000 r (HVL 0.6 mm. Al) was given to a crusted, hyperkeratotic, pigmented area 2 cm. lateral to the right ala nasi, with a good

Fig. 3 (Case 1).—Jan. 11, 1958.

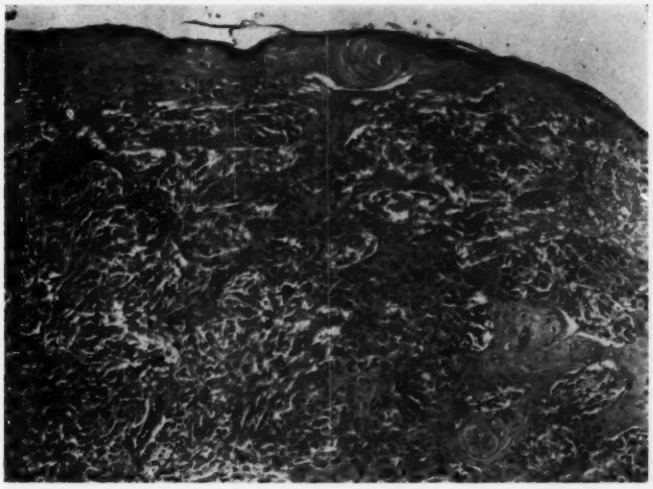


Fig. 4 (Case 1).—"Melanoma of Utmost Malignancy." (Diagnosis of Fred D. Weidman, M.D.) There is no evidence of a preceding dermoepidermal nevus.

cosmetic result. The pigmented portion now measured 8 cm. by 5 cm.

The patient was seen on Jan. 11, 1958, with progressive pigmentation and a small hyperkeratotic area in the center of the lesion, which now measured 9 cm. by 6 cm. (Fig. 3). This lesion has now been slowly evolving for 16 years.

Biopsy Report (Fred D. Weidman, M.D., 1951)

"In the sections, a melanoma of the utmost malignancy is exhibited (Case 1 [Fig. 4]). At one or two places the epidermis is still present, more or less ulcerated. There is not any evidence of a preceding dermoepidermal nevus; in fact, the tumor cells appear to be continuous with the epidermal ones, and accordingly there might be some justification for designating the lesion as a melanocarcinoma.

"In any event, the tumor consists of cells which are solidly packed and distributed diffusely, without any alveolar patterning. If there is any patterning at all, it is in the form of interlacing, vaguely indicated bundles.

"The tumor cells are for the most part undifferentiated polygonal or spindle forms which could be those of either an anaplastic squamous-cell cancer or malignant melanoma. It is possible to discover, though, certain cells which have rarefied cytoplasm, and yet others which contain goodly quantities of pigment. The nuclei are of the usual large and hyperchromatic kind which characterizes malignancy, but mitotic figures are relatively uncommon but by no means difficult to identify."

Case 2.—An 85-year-old white housewife from Lenox Hill Hospital was initially seen on March 8, 1957, for a roughly rectangular lesion 1 cm. lateral to and extending inferiorly from the left commissure of the mouth. It had been present for six years, doubling in size the preceding two years, and measured 2 mm. by 4 mm. (Fig. 5). Because of the patient's debility and congestive heart failure it was not feasible to perform a biopsy, and she unfortunately died of heart failure before one could be obtained.

The irregularly bordered, macular, noninfiltrated lesion showed a central jet-black area 1 mm. by 1 mm., bounded inferiorly by two areas 1 mm. in diameter, sepia in color, which gradually blended into a light tan background. There was neither ulceration nor regional lymphadenopathy.

Fig. 5.—Case 2.

Fig. 6 (Case 3).—Before treatment by electrodesiccation and curettage.

Fig. 7 (Case 3).—After treatment.

The clinical diagnosis was melanotic freckle without malignant melanoma.

Case 3.—A 57-year-old housewife from Lenox Hill Hospital was first seen on Nov. 11, 1957, for an irregularly bordered, nonelevated, T-shaped lesion encompassing and extending temporally from the lateral third of the right eyebrow. The macular, nonindurated area, 4 cm. in diameter, had been present for five years and had progressively enlarged with a changing pigmentary process as shown in Figure 6. Infiltration, ulceration, and regional lymphadenopathy were not present.

Clinically, the diagnosis was melanotic freckle without malignant melanoma. After a biopsy specimen was taken from two separate areas, the lesion was treated with electrodesiccation and curettage. The result of treatment is shown in Figure 7, which was taken six months later. Note that adjacent to the superior pole of the treated area hyperpigmentation is evident. This indicates the need for treating an adequate margin of normal surrounding skin.

Biopsy A (Fig. 8) *from Upper Pole* (S. Bhattacharji, M.D.)

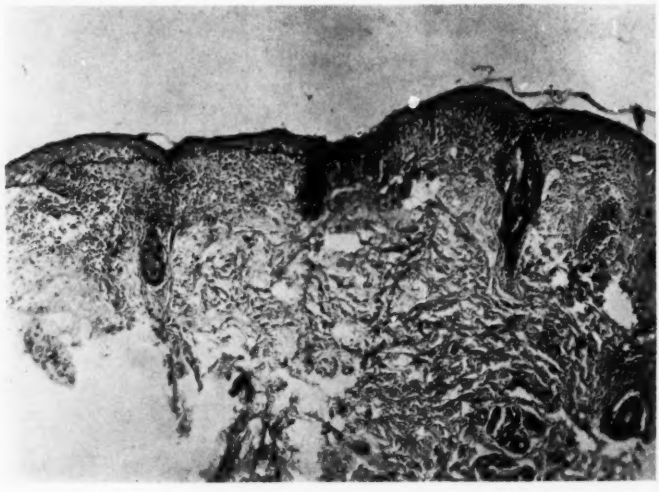


Fig. 8 (Case 3), Biopsy A.—Small foci of nevus cells in the epidermis containing pigment with heavy lymphocytic infiltration.

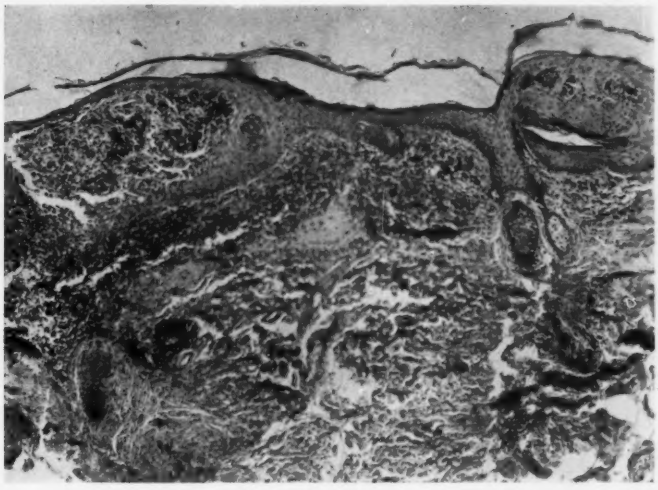


Fig. 9 (Case 3), Biopsy B.—Basal-cell layer of epidermis shows vacuolization of cytoplasm. Heavy lymphocytic infiltration of dermis. Diagnosis: Pigmented epithelial nevus (S. Bhattacharji, M.D.).

"The surface is covered by stratified squamous epithelium. There are scattered small foci of nevus cells in the epidermis and dermis, some containing yellowish-brown pigment. In the underlying dermis there is a moderate to heavy lymphocytic infiltration throughout with scattered macrophages containing yellowish-brown pigment."

Biopsy B (Fig. 9) *from Lower Pole*

"This reveals an intact epidermis throughout. The basal layer of the epidermis shows in some areas vacuolization of the cytoplasm. There is a heavy lymphocytic infiltration of the dermis throughout, with scattered macrophages containing yellowish-brown pigment. Impression: Pigmented epithelial nevus."

CASE 4.—A 72-year-old white housewife from private practice was seen on Oct. 25, 1956, because of the lesion on the right side of the nose shown in Figure 10. This had been present for 30 years. The lesion had scalloped edges with variegated sepia to jet-black pigmentation, and it contained two elevated verrucous lesions 1 mm. in diameter. There were two adjacent macular satellite lesions of the same size located superiorly and laterally. A biopsy was performed. The clinical impression was melanotic freckle without malignant melanoma.

The lesion was destroyed by electrodesiccation and curettage. Several intradermal nevi were removed from her face on a subsequent visit. Figure 11 was taken six months later.

Biopsy Report (Fig. 12, Wilbert and Perry Sachs, M.D.)

"The epidermis is somewhat flattened. Within the upper cutis is a pronounced cellular reaction containing pigment and chromatophores. However, in a few areas within the epidermis, there are nevus cells containing a great amount of pigment. There is a junction nevus present. However, due to an occasional large nucleus and the presence of a pronounced inflammatory reaction, I should suggest that this lesion be thoroughly and adequately removed. Treat as an early nevocarcinoma."

Diagnosis: Early nevocarcinoma.

CASE 5.—A 63-year-old nun from private practice was first seen on Oct. 24, 1957, for an L-shaped lesion that had been present for seven years on the medial aspect of the left foot, 3 cm. below the medial malleolus and extending 4 cm. posteriorly. At each end of the lesion elevated nodules 1 mm. in diameter were seen. By transillumination these appeared to be intimately connected to the

Fig. 10 (Case 4).—Before electric cautery and curettage.

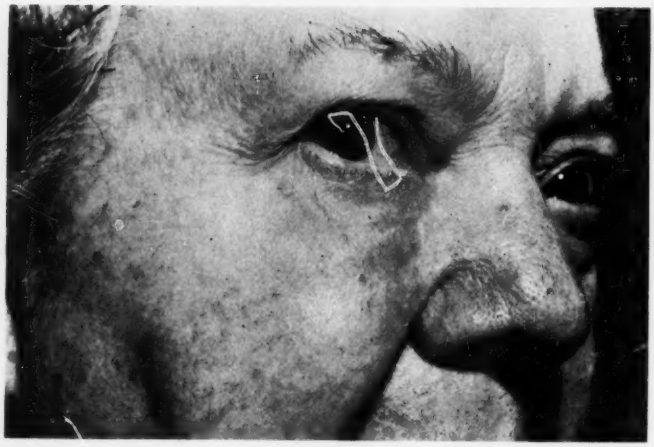


Fig. 11 (Case 4).—After treatment. Nevi were also removed.

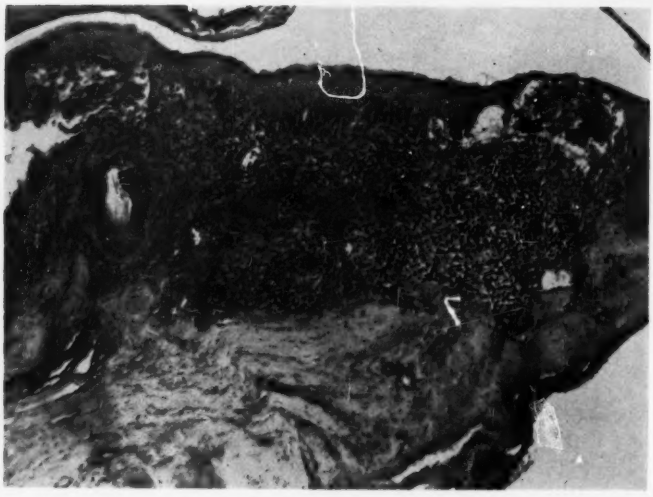


Fig. 12 (Case 4).—Nevus cells containing a great amount of pigmeht. There is a junction nevus present. Diagnosis: Early nevocarcinoma. (W. & P. Sachs, M.D.)

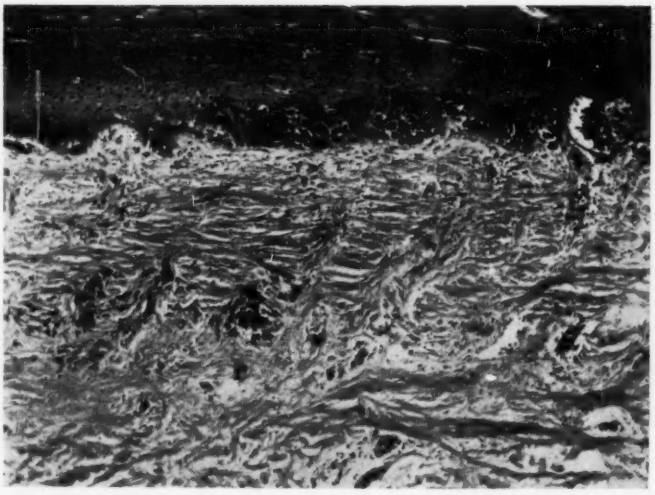


Fig. 13 (Case 5).—(Low-Power) Along junctional rims of about one-third of the epithelial layer are seen nests of cells with irregular nuclei and containing some coarse melanin pigment. Diagnosis: Active junction nevus of foot with early atypical changes. (J. M. Ravid, M.D.)

Fig. 14 (Case 5).—(High-Power). The nuclei are in places hyperchromatic and somewhat irregular, but no mitotic figures are seen.

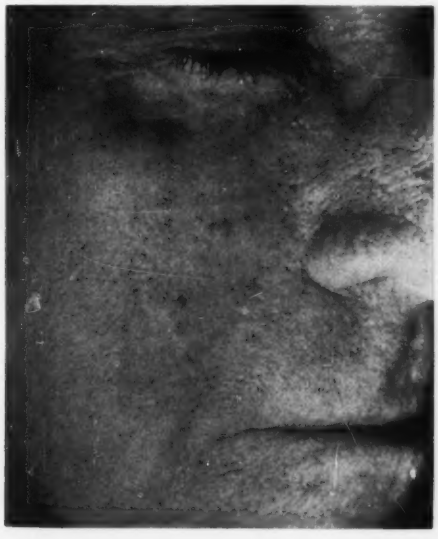
main lesion by fine, dark, thread-like strands. One nodule was light tan and the other jet-black in color, while the main lesion was an admixture of grey to black to sepia. A thin, micaceous, grey-black, easily removable scale covered the entire lesion. No inguinal adenopathy or metastatic lesions were noted. Clinically the diagnosis was melanotic freckle with questionable malignant melanoma. The lesion was excised surgically and a full-thickness graft from the right arm utilized with a good functional result.

Biopsy (Figs. 13 and 14, J. M. Ravid, M.D.)

"The specimen is covered with a dense layer of keratinized matter. Along the junctional rims of about one-third of the epithelial layer are seen nests of cells with irregular nuclei and containing some coarse melanin pigment. Within the papillary zones are also seen clumps of similar melanin containing polyhedral cells, which in places are surrounded by a rim of epithelial cells forming an island within it. Some of these cellular aggregates show a loosening in places. The nuclei

Fig. 15 (Case 6).—Before treatment.

Fig. 16 (Case 6).—Two months after electric cautery and curettage.



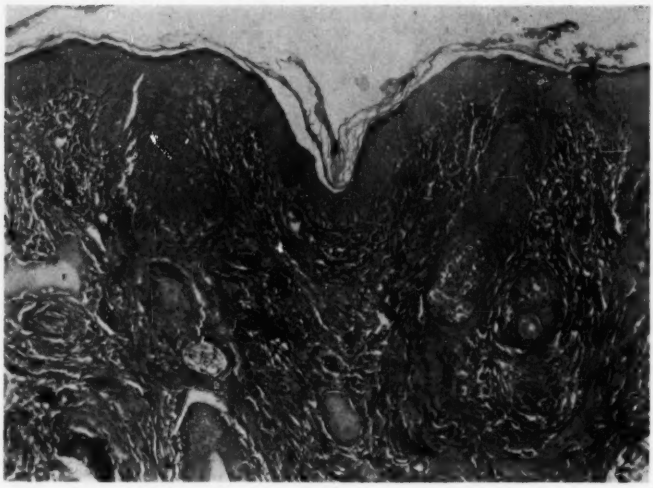


Fig. 17 (Case 6).—(Biopsy Section 1. Superior lesion of 3 years' duration) Diagnosis: Benign lentigenous lesion. (Arthur B. Hyman, M.D.)

are in places hyperchromatic and somewhat irregular, but no mitotic figures are seen."

Diagnosis: Active junctional nevus of foot with early atypical changes.

CASE 6.—A 76-year-old white delivery man from private practice was first seen on Jan. 29, 1958. He presented a hyperpigmented lesion inferolateral to the right nasogenial fold. This had been present for 8 years, enlarging gradually (Fig. 15). The two macules comprising the lesion were connected by a thin, hyperpigmented strand. The inferior, more deeply pigmented lesion was the original one, and measured 4 cm. by 2 cm. It was fairly sharply marginated, and its color was variegated. No induration, erosion, or excrescences were present. A subtotal punch biopsy was performed on both lesions (Biopsies 1 and 2). No regional lymphadenopathy was noted. The clinical impression was melanotic freckle without malignant degeneration. One week later the entire lesion was destroyed by electrodesiccation and curettage. Figure 16 was taken two months later.

Biopsy (Arthur B. Hyman, M.D.)

1. (Fig. 17, Superior Lesion of Three Years' Duration). "This piece shows a deposit of pigment in the basal zone lighter than in No. 2. There are junction theques, and the cutis shows no nevus islets, but there are strands of banal inflammation. There is no evidence of malignancy."

Diagnosis: Benign lentiginous lesion.

2. (Fig. 18, Inferior Lesion of Eight Years' Duration): "The epidermis shows heavy deposit

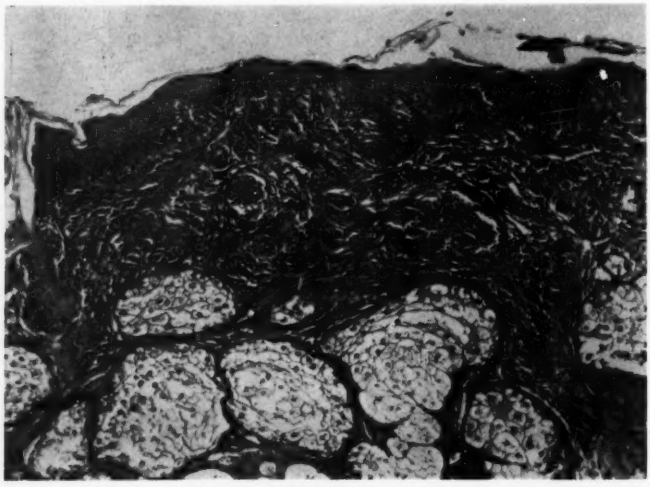


Fig. 18 (Case 6).—(Biopsy Section 2. Superior lesion of 8 years' duration) Diagnosis: Junctional nevus with some intradermal elements. (Arthur B. Hyman, M.D.)

Fig. 19 (Case 7).—Small lesion on back.

of pigment in the basal zone and there are some junction theques at the tips of the rete pegs. The upper cutis shows many islets of nevus cells. Inflammation is minimal and there is no evidence of malignancy."

Diagnosis: Junctional nevus with some intradermal elements.

CASE 7.—A 56-year-old priest from private practice was seen initially on Nov. 13, 1957, with an irregularly bordered, roughly round, slowly enlarging macule, 3.5 cm. in diameter, over the left scapula. The lesion was macular throughout, had been present for five years, and its color varied from tan, dark brown, mahogany, to gray, with one minute jet-black peripheral area (Fig. 19). The clinical impression was melanotic freckle without malignant degeneration. The entire lesion was excised surgically with an excellent cosmetic result.

Biopsy (Arthur B. Hyman, M.D.)

Section A (Fig. 20) "shows normal epidermis to each side, while toward the center there is extensive junction activity with theque formation and pigment. The subjacent cutis is edematous with foci of inflammatory reaction No invasion of the cutis is seen."

Section B (Fig. 21) "shows a similar picture near one edge, but the theques are better formed. The underlying cutis shows heavier chromatophoric pigment."

"Section C shows the least change, though nevus theque formation is seen, with edema and mild inflammation in the upper cutis."

Diagnosis: Melanotic freckle without evidence of frank malignancy in the tissue examined.

CASE 8.—A 63-year-old white executive, a patient of Dr. Henry Sarason from his private practice, was initially seen on July 2, 1957, for a lesion that had been present for 15 years (Fig. 22). It was located over the deltoid region of the right upper arm and had progressively enlarged. It was roughly rectangular, measuring 4 cm. by 3 cm. wide, with an irregular border. The general appearance was a mottled tan to dark brown with two obvious jet-black indurated areas. The largest area, which was round and measured 1 mm. by 1 mm., had a biopsy performed (Biopsy 1). The clinical impression was melanotic freckle without malignant degeneration. There was no evi-

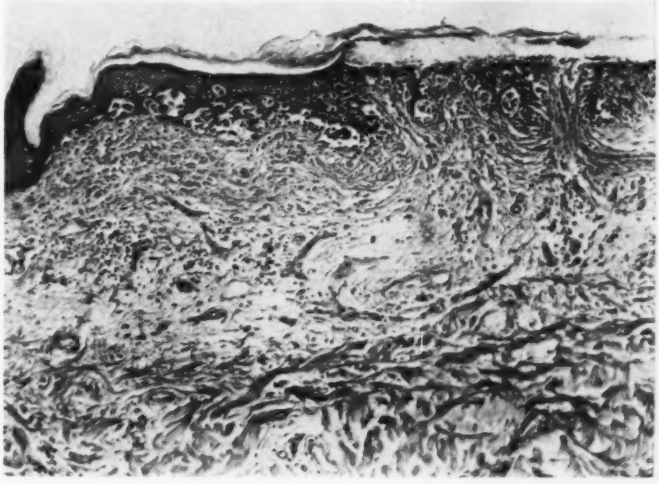


Fig. 20 (Case 7).—(Section A). Extensive junction activity with theque formation and pigment. The subjacent cutis is edematous with foci of inflammatory reaction. Diagnosis: Melanotic freckle without evidence of frank malignancy. (A. B. Hyman, M.D.)

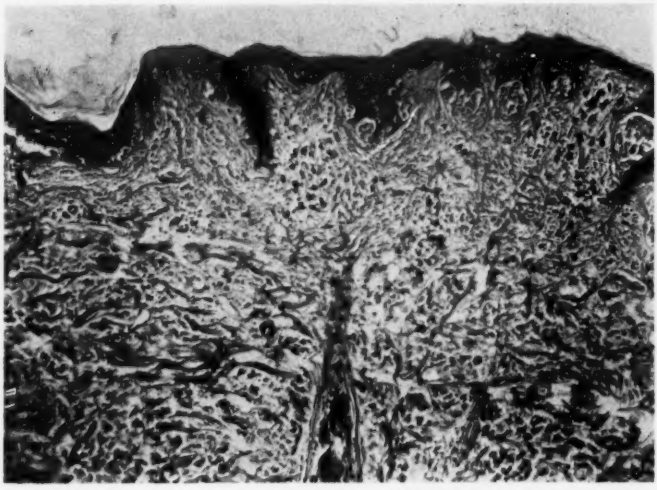


Fig. 21 (Case 7).—(Section B). Shows a similar picture near one edge, but the theques are better formed. The cutis shows more dense chromatophoric pigment.

dence of metastases. The entire lesion was surgically excised with good result (Biopsy 2).

Biopsy (Wilbert and Perry Sachs, M.D.)

"Throughout the upper cutis is a mass of nevus cells arranged in small lobes and containing a tremendous amount of pigment. Within the epidermis are groups of these cells and there is a great amount of pigment. While the picture is that of a junction nevus, I should suggest that this lesion be thoroughly and adequately removed or destroyed, if not already done."

Diagnosis: Junction Nevus.

CASE 9.—A 45-year-old white housewife from private practice was originally seen on May 1, 1958, for a lesion whose presence had definitely been noted for 21 months. The patient felt, however, that a lesion had been present in this area all her life. The lesion was located in the left paravertebral region medial to the middle portion of the left scapula. It was round, measuring 2.5 cm. in diameter, and contained a 1 mm. by 1 mm. central oval slate-gray area. The border was

Fig. 22 (Case 8).—Note round, irregular area of jet-black hyperpigmentation, the change which suggests melanomatous characteristics.

Fig. 23.—Case 9.

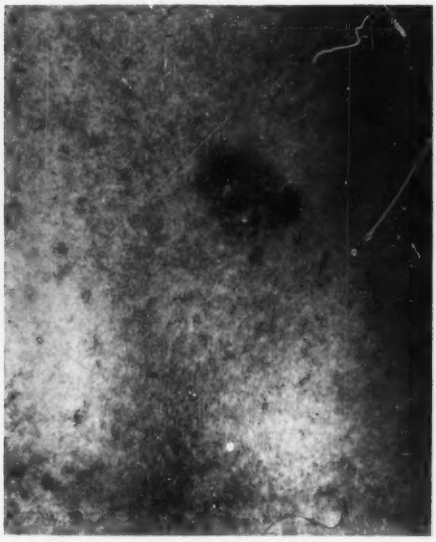


Fig. 24.—Case 10.

composed of a jet-black crust overlying the hyperpigmentation which appeared to be superficial (Fig. 23). Superior to the lesion was a dome-shaped, hypopigmented area from which a deeply pigmented crust had been removed one year previously. The area had neither bled nor increased in size. There was no induration or evidence of regional or systemic metastases. The clinical impression was melanotic freckle without malignant degeneration. A subtotal punch biopsy was performed (Biopsy 1). Subsequently, the lesion was surgically excised with a one-half inch margin of normal surrounding skin (Biopsy 2).

Biopsy 1 (Arthur B. Hyman, M.D.)

"The epidermis is thin, the rete pegs rather long, the junction zone shows poorly formed nevus theques with cells of nevus origin at higher levels toward one edge. There is some pigment in the uppermost cutis outside cells, and this area shows a band of banal inflammatory infiltrate. Except for the relatively small amount of pigment in the cutis, this is the picture of a "melanotic freckle."

Diagnosis: Melanotic freckle.

Biopsy 2 (J. M. Ravid, M.D.)

"In one area there is localized thinning of the epidermis. Beneath this there is seen a cluster of cells. The epithelial lining of the latter shows no definite orientation. The cytoplasm is scanty, pink-blue staining, and the nuclei show a hyperchromatism and clear morphism. Nests of these cells are seen also within the epidermis along the edges of the neoplastic cells and continuous with the basal layer of cells in the rete pegs and the basal cells of the epidermis. A rare mitotic figure is seen. No extension of the neoplastic cells is seen into the deeper tissue. However, clusters of tumor cells are seen extending laterally along it beneath the epithelial lining and adjacent to the basal layer of cells. Large and small collections of dark brown pigment are seen within the cells, both superficially and in other areas. Some of these cells are completely replaced by the blackish-brown pigment. In other areas, these appear to be granular. Narrow zones of lymphocytes are seen infiltrated around the tumor cells in the deeper layers of the dermis and the subcutaneous tissue. The skin appendages are intact."

Diagnosis: Superficial malignant melanoma of the back associated with a junctional nevus.

CASE 10.—A 34-year-old white man from private practice, was originally seen on August 18, 1958, for an unrelated condition. During the course of the examination it was noted that he had a lesion 1 cm. in diameter in the region of the suprasternal notch which had been present for a number of years. The patient could not date its beginning accurately. The lesion was roughly round and exhibited a play of color ranging from slightly darker than flesh color through an almost black central area. There was a minimal amount of crusting over the portion of the lesion which was darkest. There was also some slight elevation of this lesion so that it could be felt but was not infiltrated. It was our clinical diagnosis that this was a melanotic freckle. There was no regional lymph adenopathy, nor had the lesion increased in size or bled recently. The entire lesion was surgically excised and the wound closed primarily with the use of sutures, allowing a border which was roughly one-half the size of the original lesion.

Biopsy (Arthur B. Hyman, M.D.)

"Several sections were cut through the lesion. The slightly smaller piece is diagnostic. The thin epidermis shows widespread and poorly formed junctional theques, with great nuclear variety, poor adhesion, mitotic figures, pigment, and invasion of the epidermis itself. The uppermost cutis shows pigment scattered, and in one area where the cells of nevus origin grow down, there is heavy adjacent inflammation.

Diagnosis: Melanotic freckle of Hutchinson with malignant changes.

Summary

Melanotic freckle is an easily recognizable pigmented precancerous macule frequently seen on the face of patients over forty years of age. It usually exhibits a histopathologic picture resembling a premalignant junction nevus, which can slowly progress to a tumor stage showing histo-

pathologic features of malignant melanoma.

The histologic appearance is dependent on the area of the lesion biopsied. Multiple subtotal biopsies of serial examination of the entire lesion will provide a more accurate interpretation.

Individualized treatment consisting of surgical excision or electrodesiccation and curettage will provide good therapeutic, cosmetic, and functional results.

Long-term observation of patients with this clinically distinctive lesion is necessary to corroborate the impression that the prognosis of a patient with a melanotic freckle is more favorable when compared with that of a patient with classic malignant melanoma.

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ABSTRACT OF DISCUSSION

DR. MARCUS R. CARO, Chicago: Considered statistically, melanotic freckle (lentigo maligna) carries a more favorable prognosis than does a frank malignant melanoma. Dr. Costello and his associates have stressed that individualized treatment consisting of surgical excision or electrodesiccation and curettage will provide good therapeutic, cosmetic, and functional results. By the use of these measures, if care is taken to remove all traces of the lesion, both microscopic and gross, the interests of the patient will be served well, and in Dr. Costello's hands, I am certain that they are.

For operators less experienced and skilled, however, there is an inherent danger in the use of any therapeutic measures that are based upon the premise that lesions of melanotic freckle are relatively safe. Conservative treatment that may fail to eradicate the lesion completely is, in effect, a wager that there will not be a local malignant recurrence or a metastasis during the remaining life-span of the patient, and one is gambling that the patient will die of other causes before he can succumb to a melanotic disaster.

It has been aptly stated that all generalizations are false, including this one. Nevertheless, over the years I have gained the impression that malignant tumors in older patients behave rather differently than they do in younger persons. Carcinomas of the skin grow more slowly in the aged and produce peculiar histopathologic features, and even malignant melanomas here tend to be less wild. In keeping with this diminished lawlessness of tumors in old people, melanotic freckle generally behaves less aggressively than does malignant melanoma in younger patients, and it respects the neighboring tissues for a longer period of time.

Nevertheless, in any individual patient, there is constantly present the potential for a malignant supervention in the lesion of melanotic freckle, with subsequent invasion of surrounding tissues, blood vessels, and lymphatics, and with eventual metastasis. One should, therefore, accord to these lesions the same fearful respect and therapeutic thoroughness that are given to a malignant melanoma. To do less is to risk transforming a patient with a lesion that is curable into a statistic waiting to be recorded in the mortality table.

In order to make certain that the lesion is actually one of melanotic freckle, a biopsy is essential. Especially when the lesion is enlarging, becoming more elevated, or is changing in color, surface, or consistency, it is important to differentiate it histopathologically from seborrheic keratosis, senile keratosis, epidermoid carcinoma, pigmented basal-cell epithelioma or, most important, from a malignant melanoma. In the last, great

care must be taken to do nothing that may disseminate tumor cells. In highly malignant melanomas there is invasion of the vessel walls. Manipulation, such as curettage of a malignant melanoma, may release some of the tumor cells and start them on their journey to distant parts. Amadon (Amadon, P. D.: Electrocoagulation of the Melanoma and Its Dangers, *Surg. Gynec. & Obst.* 56:943, 1933) reported 27 cases of malignant melanoma treated by electrocoagulation with metastasis and death in all. In addition, Mohs (Mohs, F.: Chemosurgery in Cancer, Gangrene and Infections, Springfield, Ill., Charles C Thomas, Publisher, 1956, page 168) has cautioned that electrosurgical treatment that produces heat in a malignant melanoma may produce enough tissue steam to disrupt the fragile tissue and to propel clumps of cells into the vessels.

Because of these considerations, it would seem that melanotic freckle would be an ideal lesion for treatment by chemosurgery. As you all know, in this procedure tissue is removed after fixation by zinc chloride paste, and there is no cutting or other manipulation except on tissue that has already been devitalized. In addition, one has histopathologic confirmation of the diagnosis from all parts of the lesion, and the type of tumor and the degree of activity may vary in different areas.

Finally, by utilizing the microscopic control of chemosurgical removal one can remove all of the tumor and all of the premalignant lentigo with the least possible destruction of the affected skin. Particularly on the face is this important, so that one may produce the least deforming scar possible consistent with a complete eradication of the lesion.

Dr. Costello and his associates have produced good evidence that considerable time may elapse between the onset of a melanotic freckle and its final transformation into a malignant melanoma. In the management of an individual patient, nevertheless, one should guard against undue optimism and should make certain that a correct histopathologic diagnosis is established, and that all traces of the lesion are removed.

DR. WALTER F. LEVER, Boston: I agree that lentigo maligna deserves consideration as a distinct entity among the melanotic tumors. However, I am hesitant to include under lentigo maligna lesions located in areas not exposed to light. My feeling is that in lentigo maligna with its relatively benign course exposure to the sun over many years is an important factor. Prolonged exposure to sun, by promoting aging of the skin, may well be responsible for the relatively benign clinical course of lentigo maligna in spite of its malignant histologic picture.

As far as therapy is concerned, I should like to mention that Miescher and many of his European colleagues routinely use Grenz rays in the treatment of lentigo maligna and have reported very good results (*Arch. Dermat. u. Syph.* 200:215, 1955).

DR. SAMUEL W. BECKER, (Long Beach, Calif.): I prefer to call these lesions "lentigo maligna." Rabello uses the designation "melanosis maligna," which has the same connotation. Algernon Reese called such lesions on the conjunctiva "melanosis" and stated that they are regarded as obligative premalignant lesions. Miescher stated that they may occasionally disappear with atrophy, which I have never seen.

A potential danger of such disorders on the cheek was shown in a patient now at the VA Hospital in Long Beach, aged 72, who, in July, 1951, noted a dark spot on the left cheek, about the size of a blackhead. It slowly increased until, at the end of the third year, it was 0.5 cm. in diameter and was elevated, which portends metastasis. (Handley, W. S.: The Hunterian Lecture on the Pathology of Melanotic Growths in Relation to their Operative Treatment, *Lancet.* 1:927 and 996, 1907)

It was excised at the Corona Naval Hospital, with a pathologic diagnosis of melanoma, but lymph nodes were not resected. He was observed by the Tumor Board for two years, at which time he developed an enlarged lymph node behind the angle of the jaw. Frozen sections at surgery showed metastatic melanoma, and radical neck excision revealed metastases. Three years later, in January, 1959, he developed signs of liver metastasis, with dark urine.

It is my policy to advise deep excision of macular lentigo maligna, with lymph node dissection for elevated tumors. I think, in this way, we can improve the prognosis of melanoma.

DR. JOSEPH V. KLAUDER, Philadelphia: I wish to express my appreciation of the excellent photographs of this disease shown by Dr. Costello. It exceeds any such presentation in the literature with which I am acquainted.

I think no discussion of the disease is complete unless it is visualized in all its manifestations: I refer to its occurrence on the conjunctiva. It appears that, next to the skin, involvement is more common on the conjunctiva; it is curious how rare it is on other mucosal surfaces; for example, in the mouth.

The clinical aspects are much the same in the conjunctiva except that the field of expansion is much limited and, for that reason, I think, it is more diffcult to make diagnosis on the conjunctiva. The pigmentation has a fine granular appearance and often shows spontaneous waxing and waning. The lesion may be single, or multiple, of various sizes and configuration.

I have been interested in knowing whether the prognosis is different on the conjunctiva, whether it is more malignant, and whether it presents a

greater problem to the surgeon. It is difficult to obtain this information from the literature.

There is a confusion of names in ophthalmologic literature in designation of melanosis of the conjunctiva in which category the melanotic freckle is discussed. This familiar name to the dermatologist is rarely mentioned in ophthalmologic literature. Reese, for example, designates melanotic freckle as precancerous melanosis and in the malignant phase as cancerous melanosis.

I may now quote from my paper now in press: Melanosis of the conjunctiva has been notably studied by Reese, an ophthalmologist in New York City, and by Greer, likewise an ophthalmologist, in London.

Of 134 cases of melanoma of the conjunctiva studied by Reese, 37 were precancerous melanosis, 64 were malignant melanosis, 28 were malignant arising from a nevus, 5 were malignant; whether their origin was from precancerous melanosis or from nevi could not be determined.

Greer's experience in study of melanosis of the conjunctiva differs from that of Reese. Of 153 pigmented lesions; 118 were nevi, 30 were malignant melanomas, 5 were precancerous melanosis. Of the 30 malignant lesions, 3 showed histologic evidence of nevus origin, 9 showed such evidence of arising from precancerous melanosis, and 18 showed no histologic evidence suggesting their origin. Greer concludes that precancerous melanosis is a rare condition and does not always become malignant. Malignancy arising from a conjunctival nevus probably occurs more often than Reese has suggested.

This experience of Greer is somewhat in conformity with the origin of malignant melanomas of the skin. The melanotic freckle is a rare source of malignancy in comparison with its origin from the junctional type of pigmented nevi.

Dr. Hamilton Montgomery, Rochester, Minn.: I know that there are two schools of thought regarding the origin of the malignant melanoma cell and that Arthur C. Allen and others from the Memorial Hospital Group in New York talk of melanocarcinoma and of nevoid carcinoma. The majority of opinion, however, would support the concept advanced through the studies of Lerner, Fitzpatrick, Sam Becker Jr. and many others showing that cells in benign and malignant melanomas are not of epidermal origin, but are melanocytes of neuralcrest origin. Hence, the use of the terms benign and malignant melanomas seems to be preferable.

I agree that some of the lentigo malignas or melanotic freckles are benign, and some are malignant, and when one has a large plaque that is growing rapidly it may be necessary to have more than one specimen for biopsy, or at least take multiple sections through the block of tissue. I wish to cite the case of a so-called juvenile melanoma developing in adult life in a nurse as a solitary lesion which histologically had the criteria of a juvenile melanoma; yet that nurse died two years later with metastases even though a wide excision had been performed. Further sections from the original biopsy revealed small areas of malignant melanoma. It is important to correlate the clinical with the pathologic findings.

Dr. Francis A. Ellis, Baltimore: I just wonder whether the dermatohistopathologists will agree that, certainly, in the early malignant melanomas, you cannot differentiate them histologically from malignant freckle.

I also wish to tell you about a case of a man who had one of these for ten years and is now dying, at the age of 81, from generalized metastases.

Thirdly, I cannot believe that Mohs' method should go down as the ideal method of choice. I am not an expert on Mohs' method, but, as I understand it, with large lesions like basal-cell epitheliomas, the first thing to do is to curette out or get rid of most of the lesions. Not only that, but if you apply Mohs' paste, you get a tremendous inflammatory zone about it that will open up your blood vessels and possibly help to give you metastasis.

Dr. Victor H. Witten, New York: At our combined tumor conference, which meets at the New York Skin and Cancer Unit each week, and where we have present dermatologists, surgeons, pathologists, and radiologists, to discuss the diagnoses and management of problem tumors of the skin and visible mucous membranes, cases such as these presented by Dr. Costello are among the ones seen. We have been able in such cases, I believe, to teach the surgeons something about which they were not previously familar; that is, that these lesions are not out-and-out maligant melanomas and that they do not have to be radically excised.

Today, if such a lesion is small, our surgeons are usually satisfied to excise it with but a small margin of clinically normal tissue. On occasion one will even agree to such a lesion's being electrodesiccated and curetted, which I guess heretofore would have been heresy in the field of surgery.

It is only because Dr. Sulzberger, Dr. Alfred W. Kopf, and I recently prepared a paper on this subject which is now in press that I have the following facts at the tip of my tongue.

Because of the controversy regarding terminology which has already arisen, we should like to propose the second of the original terms used by Dubreuilh for this entity. It was in 1894 that he called this lesion "lentigo maligna of old people"; in 1912, when he presented 32 such cases, he changed the term to "circumscribed precancerous

melanosis." He did so on the basis that they occurred in young people (40 years is the average age) and that these lesions were a precancer and not a malignant melanoma, in the true sense of the word, as was pointed out today.

I must admit that the term "circumscribed precancerous melanosis" is a mouthful, and that it is much easier to say "melanotic freckle" or "lentigo maligna," but for the reasons mentioned, we feel that the term "circumscribed precancerous melanosis" is a better term for these lesions and will cause less confusion than the others currently in use.

At times there may be difficulty in distinguishing the early circumscribed precancerous melanosis from a well-developed senile lentigo, as described by Cawley and Curtis.

DR. EUGENE F. TRAUB, New York: I am happy that Dr. Costello included lentigo maligna as a variety of junction nevus. This is where we (Traub, and Keil: The Common Mole: Its Clinicopathologic Relations and the Question of Malignant Degeneration, *Arch. Dermat. & Syph.* 41: 214, 1940) classified them originally. Since then there has been some considerable controversy on this point, as some had stated that definitely junctional activity in these lesions ruled them out as lentigo maligna.

When I had seen all of Dr. Costello's photographs this morning, this seemed to be a lesion in which the differential diagnosis should not be difficult. One lesion that was not mentioned in the differential diagnosis that might be confused is Block's benign pigmented epithelial nevus in which the pigment is entirely epidermal. Since it occurs in the aged and runs a relatively slow and benign course, it might be mistaken. However, they are found more commonly on the body rather than the face.

There is one other lesion that also might be confused. Rarely, a blue nevus is brown in color and has a few dark-bluish changes which might be interpreted as a possible change in consistency of the lesion. Of course, microscopically, the blue nevus is so distinctive that there could be no difficulty in differential diagnosis from the microscopic standpoint.

Another point that Dr. Costello, perhaps, did not have time to stress is this, that the difficulty in evaluating malignancy of these lesions is based on the fact that the histopathology is confusing. An actively growing junction nevus is very often interpreted by the average pathologist, or even the skin pathologist, as an active melanoma or a malignant melanoma. The clinician knowing by experience the usual course of these tumors is in a better position to evaluate the malignancy than the pathologist.

We all know that these lesions in older people are more slow-growing. It is exactly like the so-called juvenile melanoma in young people. For some reason or other, when a junction nevus occurs early in life or late in life, the prognosis is much better.

The treatment that Dr. Costello has outlined is, in the main, the correct one. I do not believe, by and large, we need to remove these lesions too radically. I think that his treatment as suggested is the correct one, because of the confusion among the pathologists in believing these relatively mildly malignant lesions to be much more malignant than they actually are.

DR. HERMAN V. ALLINGTON, Oakland, Calif.: I appreciated hearing this paper because I have been concerned with this type of lesion and have been performing biopsies on a number of them. I still am confused as to when one should consider these important and take active steps to treat them.

So far as I know, the early phase, clinically, is simply that of a tan or brownish macule. Microscopically, at that stage there are simply more than the usual number of clear cells or nevus cells in the basal-cell layer. As the lesions progress, these cells become greater in number. They then begin to form clumps and give the picture of a junction nevus. From there some go on to develop the picture, both clinically and microscopically, of a full-blown melanoma which we all can readily recognize.

When, in this picture, do these superficial, macular, brownish pigmented lesions become important? How does one predict their eventual behavior when they are seen in the early phase?

Chemosurgery, I believe, is at its best in the treatment of problem cases involving basal-cell epitheliomas. In the case of melanomas where spread by blood or lymph channels occurs, chemosurgery is less certain to cure. When one is in melanoma-free tissue as judged by the microscopic sections from the whole periphery of a chemosurgery wound, one still cannot be sure that lymphatic "seeding" has not taken place in any direction beyond this zone. It is usually recommended that an arbitrary margin (though there are no agreed rules as to what constitutes an adequate margin) beyond and beneath the borders of a melanoma be removed or destroyed. If this be so, then the prime advantages of chemosurgery have been lost, and the additional effort to both physician and patient involved in chemosurgery has been of little value.

I am not convinced that electrodesiccation favors dissemination in these lesions. I feel that if the same amount of tissue is removed or destroyed, chances of cure would be as good in a given lesion whether treatment had been by electrodesiccation or by surgical excision.

DR. RICHARD L. SUTTON, JR., Kansas City, Mo.: Dr. Allington said some things that I wish to elaborate upon. My contribution to the discussion will be concerned with only a small fragment of it and limited to metaphysical aspects of that fragment.

Dr. Caro said that Dr. Mohs said that applying heat to a melanoma may steam-pressure loose a malignant embolus. (Correctly used, of course, the cautery cuts through normal tissue, not tumor tissue, in an "en bloc" dissection.) What Dr. Mohs may have hypothesized is, to me, hearsay. But the way of thinking this exemplifies arouses my urge to take up the cudgel.

The way we know whether anything may happen is to see that it has happened, at least once. There is no a priori reason why, following the x-ray epilation and cure of a case of tinea capitis, the child may not become reinfected with tinea. But I have not seen it happen. This enables me to conclude safely only that, if reinfection occurs after x-ray epilation and cure, it occurs with a frequency that is not greater than a small fraction. If a coin is tossed, it may fall to stable equilibrium with heads up or with tails up, or it may come to rest in unstable equilibrium balanced on the rim, or it may be snatched in midair by a sea gull. There are other possibilities, I should guess: you may drop dead before the sequence of events has come to a conclusion, so that you never do know how it turns out.

Until a sequence has come to its conclusion, you do not know the outcome.

Now I will purposely commit the sin that I condemn. I shall hypothesize that this idea of steam-pressuring loose a malignant embolus is silly; but I stand ready to recant the instant I observe it or learn from a creditable source that it has happened.

DR. VERNON M. HENINGTON, New Orleans: I rise only to mention to this Association a new modality which we feel has real promise in the treatment of malignant melanomas.

About 1954 Bergel and Stock reported the marked tumoricidal effects of aminophenylalanine in animals. However, when given systemically it was exceedingly toxic. About 1957, Creech, Krementz, and Ryan of the Tulane and Charity Hospital Department of Surgery, thought that the toxic effects of the cancerocidal drug could be eliminated if the tumor bearing area could be isolated from the general circulation and treated. In this way, perhaps a higher concentration could be used without entering the general circulation and thus producing the general toxic effects that one gets when the mustard is given directly in the general circulation; and since there was evidence to suggest that the effects of radiation were potentiated by high oxygen tension, it was postulated that with the use of a heart-lung apparatus for profusing the tumor-bearing area the oxygen tension of the blood could be increased several times the normal level and that the propulsive force of the pumping mechanism might produce an adequate distribution of the chemotherapeutic agent throughout the involved part.

Inasmuch as nitrogen mustard remains active in blood for about five minutes and phenylalanine mustard is active for at least six hours, it was decided to give most of these patients phenylalanine by infusion.

I spoke to Dr. Krementz yesterday to get his latest figures and he tells me that to date they have treated 35 malignant melanomas by this procedure. Practically all of them have shown a definite response, and one-half of this number have remained fully controlled to the present time. He also states, interestingly enough, that when patients have a predominance of lesions, say on the right leg, and the right leg is profused—and although this is done by closed circulation—that other melanomas scattered over the body have seemed to respond. As yet he cannot account for this.

Phenylalanine is mixed with propylene-glycol in the proportion of 1.5 mg. per kilogram of body weight and profusion is continued through the part for one hour. The venous line is then discontinued and 500 cc. of blood with the mustard is drained out of the extremity. Then 500 cc. of clean blood, that is, blood removed from the patient before the procedure was begun, is put through the extremity and is then drained out. The vein and artery are then closed. Inasmuch as very large doses of the drug are given it is necessary that complete isolation of the part must be obtained, for in a few patients when the mustard got out of the closed circulation there was a marked depression of bone marrow and some patients died.

DR. MAURICE J. COSTELLO, New York, closing: I think Dr. Witten hit the nail on the head when he said that dermatologists have little difficulty in making the diagnosis of melanotic freckle clinically. We made the correct clinical diagnosis in all 14 cases presented. I do not know of any dermatological entity that shows such distinctive features.

I think that we should get this information over to the general practitioner, and especially the surgeon, who is often the first to see these people and often the first to treat them. A great deal of publicity is needed for that reason.

Dr. Becker agrees with us that melanotic freckle runs a rather benign, long course. Therefore, there is plenty of time to treat these lesions adequately and early. My impression is, since the diagnosis is easy to make, that treatment should be administered promptly. The confusion and difficulty in

confirmation of diagnosis lies, as I see it, in the hands of the histopathologists. This is readily understood, because the histopathologic picture changes and is conditioned by so many things—by the age of the lesion, infiltration, the pigmentation, the place from which the biopsy is taken, and so forth.

We had a number of dermatopathologists and several histopathologists examine these slides. The correct definitive diagnosis was not made in one case. A woman is still living of whom the pathologist said that she had a "melanoma of the utmost malignancy;" and I believe it is unwise for the histopathologist to report: "This lesion appears to be a junction nevus, with some activity. I should advise that it be treated like a nevocarcinoma." That places the physician in an unenviable position medicolegally. Other diagnoses suggested by histopathologists were benign lentiginous junction nevus with intradermal melanotic freckle, superficial melanocarcinoma, malignant melanoma, and so on.

The ages in our cases were between 32 and 90 years. I believe that even when these lesions metastasize, they are not rapidly malignant.

Chemosurgery of Dr. Mohs certainly suggests itself to me as a method of treating these lesions, and I mentioned it in our paper. Melanotic lesions that are not malignant freckles usually run a more rapid course, as the one I showed you a moment ago—the patient with the lesion on the back, which was diagnosed incorrectly histologically as a melanotic freckle. I think it is a melanocarcinoma, because it has no play of color and there was great rapidity in the course of the eruption.

Keloids: Etiology, and Management by Excision and Intensive Prophylactic Radiation

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Julius Jadassohn's classification of keloids into the "true" (spontaneous) and "false" (traumatic) variety [1] would seem unduly meticulous to modern dermatologists, but most of them would still subscribe to his statement that excision followed by irradiation is the treatment of choice. Flurries of interest in such procedures as infiltration with hyaluronidase, corticotropin (ACTH), and hydrocortisone; freezing; dermabrasion, and others have ended largely in disappointment.

Little has been published since Belisario's detailed review of the literature in 1957 [2] (except for Kelley and Pinkus's article on tetrahydroxyquinone, which is mainly for inoperable cases [3]) to warrant special mention here. In Belisario's series of 114 lesions, excision and irradiation preceded by infiltration with hyaluronidase (150 units per ml.), hydrocortisone (25 mg. per ml.), or both, gave better results than excision and irradiation alone. Of 30 cases treated in this way, 17 achieved a cosmetically satisfactory result, and 24 had the keloid eliminated. The dose of x-ray was 400 r monthly for three doses, or 200 r fortnightly for up to six doses, or 150 r weekly up to eight doses. Results with this technique, either alone or following surgery, were unsatisfactory in the great majority of his cases.

The 179 keloids (in 155 patients) on which this report is based occurred in a variety of races, as a result of a variety of causes, and were treated in a variety of ways, the comparison of which provides some points of interest.

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TABLE 1.—*Sex and Race of Keloid Patients*

	Caucasian	Japanese	Chinese	Other	Total
Male	19	14	11	5	49
Female	44	31	14	17	106
Total	63	45	25	22	155
Per cent *	39%	30%	20%	11%	
Expected *	40%	35%	10%		

* Arnold's cases only

Sex and Race

Table 1 shows the number and proportion of lesions occurring in Caucasian, Chinese and Japanese patients. The only disproportion in sex incidence was that resulting from the many laparotomy scars following gynecologic procedures (Table 2). The supposed prevalence of keloids among Japanese patients, which has long been thought to exist, proved to be an illusion: only the expected proportion was found among patients of this ethnic group. Twice the expected number occurred among Chinese patients, but the numbers were not large and the significance is doubtful.

TABLE 2.—*Causes of Keloids*

	Spontaneous	Laparotomy	Misc.	Recur.	Total
Male	6	1	40	8	54
Female	15	30 †	66	13	124
Total	21	31	106	21	179

† All rectus incisions except two in a Pfannenstiel incision, two in a McBurney, two in right upper quadrant gallbladder incisions, one in a nephrectomy incision.

TABLE 3.—*Miscellaneous Causes of Keloids*

Injury		Miscellaneous Incisions	
Mechanical	11	Breast tumors	7
Burns	12	Thyroidectomy	4
Cautery	8	Thoracotomy	2
		Curettement	2
Inflammation		Graft donor site	1
Acne	16	Nephrectomy	1
Varicella	6	Unspecified	28
Vaccination	5		
Furuncles	4		

TABLE 4.—*Result of No Treatment, or Simple Excision*

	Good	Fair	Failure	Worse	Not Followed
No treatment (32 keloids)	2*	3	4	8	15
Excision only (14 keloids)	2†	1	5	6	0

* One after curettage, one in Pfannenstiel abdominal incision.
† One following cautery for destruction of a mole, one following burn in three-and-one-half-year-old child.

Various Causes

Table 2 shows the causes of these keloids. The 21 spontaneous lesions were all of the typical transverse sternal band variety, and gave no history of antecedent trauma or infection. Curiously, they were five times commoner in Japanese, and three times commoner in Chinese, than among Caucasians. The miscellaneous category, being so large, is given in detail in Table 3. It is of particular interest here to note the remarkable rarity of keloids in curettement scars, since this operation is performed several times daily in my practice. Graft donor sites are also a curiously unproductive source. The same may be said of thoracotomy, thyroidectomy, and mastotomy scars, since one of us is associated with a group whose five general surgeons perform such operations several times a day.

Results of Therapy

Table 4 indicates the outcome in 17 of 32 lesions not treated at all, and in all of 14 cases treated by excision alone. It is noteworthy that with no treatment, there was spontaneous subsidence of one keloid in a curettement scar, and one in a Pfannenstiel incision. Excision alone was successful in only 2 of 14 lesions: a cautery scar following removal of a mole, and a traumatic burn scar—both in young children. Nine of these 46 lesions were not helped, and 14 were made worse, by this approach.

Table 5 compares the results of treatment as observed after from one to twelve years. Only 11 cases were treated with hyaluronidase or hydrocortisone injections, or both, or topical applications of hydrocortisone solution or ointment. Failures outnumbered successes by five to two in the seven cases that could be followed after such treatment.

Irradiation alone was used in 67 cases, usually on inoperable lesions, or on lesions that had begun to recur after excision. "Good" results (80% to 100% success) fell short of "fair" and "failure" outcomes by a small margin when conservative radi-

TABLE 5.—*Comparison of Treatment Results*

	Cases Treated	Good	Fair	Failure	Not Followed
Miscellaneous *	11	2		5	4
X-rays only					
Conservative †	22	9	4	7	2
Vigorous ‡	45	29	4	6	6
Excision and x-rays					
Conservative	28	14	5	9	
Vigorous	24	17	2	3	2

* Hyaluronidase, cortisone, corticotropin, etc.
† 150 to 400 r weekly to three-monthly for 2 to 4 doses.
‡ 500 r every 5 days for 2 to 6 doses.

TABLE 6.—*Relation of Duration to Success of Treatment*

		Result of Treatment			
Duration	Cases	Good (80%-100%)	Fair (40%-70%)	Failure (0%-30%)	Not Followed
Over 1 yr.	63	25	7	26	5
1 mo. to 1 yr.	62	30	7	15	10
Under 1 mo.	30	19	2	5	4
Total	155	74	16	46	19

Fig. 1.—Keloid (left) recurrent after excision of postvaccination keloid following by 500 r every five days for five doses, begun two weeks later (too late). (Right) freshly-healed scar resulting from its excision and subcuticular suture.

ation techniques were employed, but exceeded them by three to one among the 45 lesions given 500 r every five days for two to six doses.

Prophylactic irradiation following surgical excision gave equal numbers of "good" and "fair" or "failure" results when conservative doses were employed, and better than three "good" results to one "fair" or "failure" when the intensive regimen was used.

Table 6 correlates the age of the keloid with the result of treatment, without reference to the type of treatment used. "Good" results were obtained in two-thirds of the keloids treated within one month of onset, and in well under half of those treated later. "Failure" was much more frequent in lesions more than a year old. This is no new observation; it merely confirms the opinion of many writers. Widening of the scar occurs fairly often despite radiation.

Technique of Irradiation

We believe it is best to excise keloids surgically, if they are to be treated at all; close the wound with minimal tension; and start prophylactic radiation therapy as soon as healing has advanced sufficiently to permit removal of all or most of the sutures (Fig. 1).

The technique preferred is 140 kilovolts, 5 milliamperes, no filter, 25 cm. distance: a half-value layer of approximately 2 mm. Al; dose, 500 r. The skin is shielded right up to the line of the incision—or, occasionally, the area of the early recurrence of keloid—with Wilson's bismuth putty (bismuth subnitrate in anhydrous lanolin, q.s. to make a stiff, but flexible, plastic putty [4]). This is done for linear lesions by rolling the putty into a cylinder half an inch or so thick and as long as the area to be treated; this cylinder is pressed flat into a ribbon perhaps an inch wide. This is cut lengthwise into two strips with a sharp knife or razor blade,

Fig. 2.—Bevelling edges of bismuth putty strips.

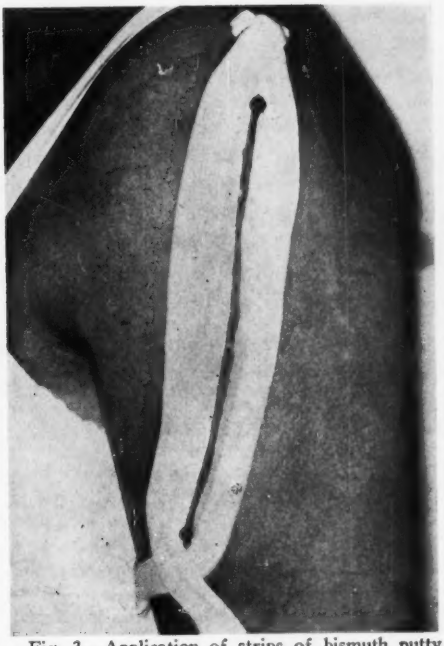

Fig. 3.—Application of strips of bismuth putty to the edges of the same incision scar shown in Figure 1.

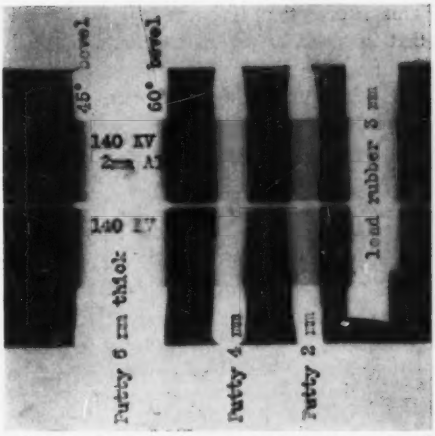

Fig. 4.—Radiograph made by delivering approximately 1 r of x-rays to a film, protected by bands of bismuth putty (from left to right) 6 mm., 4 mm., and 2 mm. thick, and a band of lead rubber 3 mm. thick; the upper and lower transverse bands received radiation generated at 60 kv. without a filter; the second band from the top received x-rays at 140 kv. with a 2 mm. Al filter; the second band from the bottom received radiation generated at 140 kv. with no filter. The widest (the 6 mm. thick) band of bismuth putty has a 45-degree bevelled edge on the left side, a 60-degree bevel on the right.

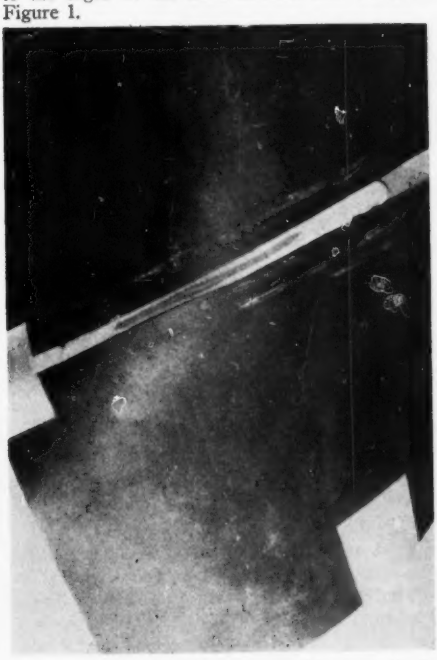

Fig. 5.—Lead rubber sheet with central slot about 1 cm. wide, laid over the putty strips.

holding the blade at a 60-degree angle, so as to bevel the edge of each strip (Fig. 2). The strips are then laid flat on the skin, bevel side up, thin edge against the edge of the incision line or the edge of the incipient keloid (Fig. 3). This permits easy, rapid, and accurate shielding of the normal skin. The effectiveness is shown in Figure 4. Over the putty is laid a sheet of lead rubber with a one-centimeter-wide opening across its middle, through which the narrower slit is exposed (Fig. 5). Smaller sheets of lead rubber laid crosswise shield the skin beyond the ends of the incision, and the exposure is then made.

The relatively generous dose of radiation —500 r, repeated every five days for two to six doses—is predicated on the fact that the very narrow field permits virtually no backscatter, thus reducing the effective tissue dose to well under an erythema unit. Two radiation physicists have concurred in the opinion that this dose is well within the range of safety and potential effectiveness.[5]

This supposition is borne out by the fact that in 69 cases irradiated thus intensively, 61 of which were followed for from one to ten years, only four instances of mild telangiectasia were seen. It is not certain that even this was a result of radiation, since telangiectasia does occur occasionally in untreated keloids.

This dose is admittedly too large to be given safely to keloids a centimeter or more in their smallest diameter. We have no rule of thumb to suggest; one must "temper the wind to the shorn lamb" and use judgment, if irradiation is to be employed without prior excision.

Summary

No ethnic predilection to form keloids was noted in 45 Japanese patients among 155 patients with keloid seen in a 10-year period. There were twice as many Chinese patients in the series as were expected on the basis of their proportion in the office population.

Keloids were produced far more commonly by midrectus or lateral rectus laparotomy incisions than by any other surgical procedure, and seldom followed cutaneous curettement, thyroidectomy, thoracotomy, or skin grafting.

Eight of seventeen untreated keloids grew worse, and four remained unimproved; among fourteen keloids which were merely excised, six returned worse than before and five were not improved.

Conservative irradiation for the alleviation of keloids was less effective than vigorous irradiation, giving twice the failure rate and only two-thirds the rate of "good" results. Approximately the same ratio prevailed when irradiation was used prophylactically after surgical excision of the keloid.

Conclusion

No keloid can be treated with complete confidence in a satisfactory outcome, and lesions which constitute no great cosmetic or functional defect, or source of serious discomfort, should probably be left alone, lest treatment merely enlarge them.

Keloids unsightly enough to be worth the risk of failure may often be successfully treated by careful surgical excision followed by 500 r of unfiltered x-rays to the incision every five days for two to six doses, starting the day the stitches are removed.

1020 Kapiolani Street (Dr. Arnold); Tripler Army Hospital, APO 438 (Col. Grauer).

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ABSTRACT OF DISCUSSION

DR. ANTHONY C. CIPOLLARO, New York: The paper by Arnold and Grauer is excellent, to the point, and thought-provoking. In their series of keloids, like other series, trauma of one kind or another is the precipitating cause. The intrinsic etiologic factors are now as mysterious as always. The incidence of keloids in the Chinese in this series appears to be greater than in Caucasians.

The skin in some regions of the body, such as the auricular, presternal, abdominal, and scapular areas, is more prone to the development of keloids, as is recorded by the authors. In other areas, keloids occur less frequently.

The authors confirm the prevailing opinion regarding the therapeutic response of keloids. They respond best to radiation alone or combined with surgical excision. Other methods, such as refrigeration, dermabrasion, injection of corticosteroids or hyaluronidase, yield generally poorer results.

Older keloids are less responsive to treatment than more recent ones. Those following electrosurgical procedures respond uniformly well when irradiation is applied soon after their appearance. For the treatment of keloids following electrosurgery, I prefer to use doses of 150 r of conventional superficial x-rays, using 60 to 100 kv. with

a half-value layer of between 0.5 and 1 mm. of aluminum given bi-monthly for a total of from four to six doses. This dosage is more intense than some of the doses which Dr. Grauer used for the treatment of some of the cases in his series; but much less intense than the 500 r dose which Dr. Arnold used in his series.

The authors employed two treatment schedules. Better results were obtained when the more intense and more vigorous treatment schedule was employed. They used moderately penetrating radiations produced with 140 kv., at a half-value layer of 2 mm. of aluminum in doses of 500 r, every five days for a maximum of six treatments, or a total of 3,000 r.

It is surprising to me that radiodermatitis did not occur more frequently with this large dose. I believe that the authors encountered radiodermatitis in only 4 cases of 60 treated. The manifestations of overirradiation were mild, manifesting essentially telangiectasia.

Even though the therapeutic response is poorer with the more conservative method of treatment, yet I prefer a dose schedule halfway between the two presented by the authors.

This is a valuable paper with contributes to our knowledge of the treatment of keloids. Keloids still pose a problem both from the standpoint of etiology and of treatment. As of now, the best treatment for keloids is x-ray therapy.

DR. J. WALTER WILSON, Los Angeles: Since the keloid originates from mesodermal tissue and not epidermal tissue, I was a little surprised at the closeness with which Dr. Arnold shields his lesions. I usually shield less closely, allowing the x-ray to be exposed to an area of at least 8 mm. in width, because I think the subcutaneous stitches that are put in, which are not visible from the surface, are the ones which produce most of the trauma which is responsible for the subsequent keloid.

If I might digress for just a minute, as long as Dr. Arnold mentioned the bismuth putty, I still use it for all shielding, and I assure you that I do not do it just out of plain stubbornness. I do it because I am too lazy to do it the hard way, by cutting pieces of sheet lead to fit. I think the main reason why most of you abandoned the original putty was its stickiness. I am glad to say that there is now available an adequate x-ray shielding putty which is not objectionably sticky.*

DR. MAURICE J. COSTELLO, New York: I certainly think that the treatment suggested by Dr. Arnold, of excision followed by roentgen ray, is good. However, I agree with Dr. Wilson that the area of irradiation or the area of exposure should be wider. I do not think you get much effect from roentgen rays administered to an area less than a quarter of an inch wide, no matter what quality of radiation you employ.

The skin, following the disappearance of keloids of any size, is never normal in appearance, no matter what the modality used for their removal. There is always widening, telangiectasia, shiny atrophic appearance, and depression beneath the nevi. It has always interested me why keloids are rarely seen below the waistline, except in abdominal scars.

We have had quite good success in the treatment of small, circumscribed keloids by application of dry ice with pressure. I might add, too, that dry ice is also effective in a condition which is seldom treated, that is, subepidermal fibrosis.

DR. HARRY L. ARNOLD JR., Honolulu, Hawaii: With respect to the point raised by Dr. Cipollaro, about the Japanese, I think that they were shown in this series not to be more prone than other racial groups. I have about 40% Japanese in my practice, and 40% Japanese among my keloid cases. No unusual predisposition seems evident there. I have only about 10% Chinese in my practice, and I had about 20% of them among the keloid series. The numbers were so small that I hesitated to attach any significance to that disproportion.

The suggestion by Dr. Cipollaro of a compromise dose seems to fit in well with the suggestions of both Dr. Wilson and Dr. Costello, that I am treating too narrow a field. I felt, when a keloid was meticulously excised and the wound gently closed surgically, the entire field of activity for the development of the keloid does lie within just a couple of millimeters on either side of the skin incision, and I was probably treating the entire area that was contributing to the delinquency of the skin. But perhaps that is not so, and the best answer may be to reduce this dose to a level that can be safely given to a field 7 or 8 mm. wide, and try it in that way.

Dr. Wilson, I think, is unduly modest about his putty. I do not think it is just a matter of saving yourself the inconvenience of trimming lead shields to fit. I do not believe it is possible to shield lesions of odd shapes and sizes precisely, and keep them shielded during a radiation exposure, in any other way except with this putty, which adheres lightly to the skin surface and follows every contour of it and stays right where you put it. There is no shifting about at all possible during the treatment, and no possibility of a leak in the sides of the shield. It is, in my judgment, indispensable, and it has many wider uses in x-ray shielding than I showed you here.

Again, I thank the discussers.

* Allergan Corp., 749 Beacon St., Los Angeles 17, Calif.

Dermatological Nomenclature

S. WILLIAM BECKER, M.S., M.D., Long Beach, Calif.

Nomenclature is defined in Webster's New International Dictionary as: "The system of names used in a particular branch of knowledge or art." According to Rattner [1] in his scholarly paper with historical review ". . . the purpose of nomenclature is to facilitate the interchange of knowledge, to be a means of scientific communication." He suggested simplification of nomenclature for undergraduate students. I should heartily agree and believe the same is valuable for the young resident in dermatology as well. Pillsbury, Shelley, and Kligman [2] have simplified nomenclature without sacrifice of clarity.

Since 1955, I have been the proud but uneasy chairman of a Committee on Nomenclature of the American Academy of Dermatology and Syphilology. Other members of the committee are: Herman Beerman, Maurice Costello, Roy Kile, Hamilton Montgomery, Herbert Rattner, and Francesco Ronchese. Credit for any achievement of the committee is due to the untiring efforts of the members, who have unselfishly given time from their busy routine for this study.

Canvass of the available nomenclatures revealed four principal ones: "A.M.A. Standard Nomenclature of Disease and Operations" [3]; "World Health Organization International Classification of Diseases" [4]; F. E. Rabello's "Nomenclatura dermatologica," [5] and a remarkable, very complete mimeographed Nomenclature by Dr. E. H. Hermans Sr., of Rotterdam, loaned to me by Dr. M. E. Obermayer. The very completeness of the last two made them valuable for reference but difficult to use in a hospital record library. The WHO Nomenclature gives multiple acceptable terms, which would be of more value for worldwide use than for local consumption. The "Standard Nomenclature of Diseases and Operations" seemed best for our purpose, because it endeavors to give one diagnosis for each dermatosis, with subheadings for sake of completeness. In case two designations are of approximately equal value, the second choice is sometimes given parenthetically.

Because of the increased use of English in international intercourse, e.g., the WHO nomenclature and the abstract journals *Excerpta Medica*, it was felt that English should be used when possible, with a full realization that the Committee on Nomenclature of the International Dermatological Congress might consider the use of the traditional Latin and Greek more feasible for their purpose. That the use of English is by no means original with our committee is evident from the statement of Howard Fox,[6] on whose committee I was privileged to serve in preparation of the third edition of the "Standard Nomenclature of Diseases": "The use of English in place of Latin or Greek terms has been the editorial policy for the entire volume." He admitted, however, that great difficulties were encountered in dermatologic and ophthalmologic names. He asked: "What English equivalents would, for instance, be suitable for acne, erysipelas, ichthyosis, scabies, scleroderma, or zoster?" If his shade is attuned, it will be pleased to know that the present committee did not change any of these terms.

In order to facilitate study of the designations in the "Standard Nomenclature of

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TABLE 1.—*Work Sheet Diagnosis from Standard Classified Nomenclature (1952)*

Term
Synonyms
Definition
Morphologic diagnosis
Etiologic diagnosis
Pathologic diagnosis
Recommendations to the committee

Diseases,"[3] a work-sheet was devised (Table 1) which was used by the members of the committee. Dermatologic diagnoses are ordinarily made on the basis of morphology, etiology, or pathology. Many of the diagnoses which confuse students and members of the medical profession have been made on morphologic features only and as yet have been unchanged. According to Williams,[7] "The source of all our woe in this respect is the fact that the etiology of many dermatoses is still unknown, and, until the problem of etiology is settled, there will be no entirely satisfactory classification and nomenclature."

Discussions of nomenclature, prior to Rattner's article,[1] are not frequent in American dermatologic literature. Two editorials appeared in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY in 1926, one, "The Curse of Many Names" by Williams,[7] the second by the editor-in-chief, Dr. W. A. Pusey.[8] Williams stated: "There are at least 38 different kinds of acne by actual count, and the worst of it is that many of them are not true acne at all, as, for instance, acne artificialis, which is caused by bromides, or iodides, or something else." Pusey, in "The Serious Obstruction to Progress in Multiplication of Names,"[8] stated that nomenclature in dermatology is not complicated compared with that of botany or chemistry, for example. He added: ". . . but a strong indictment can be brought against dermatology on the ground of multiplication of names for the same fact for the same disease to be specific." He believed that many synonyms are a real obstacle to dermatologic progress.

"The Tyranny of Words" by Williams has much to do with nomenclature. He discussed acne, eczema, seborrheic dermatitis, sarcoid, the relation between folliculitis decalvans and pseudopelade, and the use of the term "allergy." He closed by saying: "One must submit to the tyranny of words, but one can also make them one's servants and, having first formed a clear idea, one may, if one is fortunate, find words that will convey that idea to others."

Index references to articles in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY in which nomenclature is discussed were rare during Pusey's editorship, uncommon during that of Fox, but numerous from volumes 55 in 1947 to 62 in 1950, during the early part of O'Leary's term. Since then, during which time the index underwent temporary idiopathic atrophy, references to nomenclature have been infrequent. It would seem to be a worthwhile endeavor to index articles under that heading in which nomenclature is discussed as was done from 1947 to 1950.

A suggested nomenclature, classified under headings outlined by Rattner, was submitted by the Committee to the Board of Directors of the Academy in April, 1959. Recommended deletions are shown in Table 2; additions (morphologic) in Table 3; (pathologic) in Table 4; (etiologic) in Table 5; and changes in classi-

TABLE 2.—*Proposed Deletions*

Dermatitis dysmenorrheica
Erosio interdigitalis blastomycetica
[illegible]ne cerulea
Pityriasis rubra
Sarcoid, Darier-Roussy

TABLE 3.—*Proposed (Morphologic) Additions*

Acrosclerosis
Alopecia, symptomatic, due to lupus erythematosus
Cutis hyperelastica (Ehlers-Danlos)
Defect, prenatal cutaneous
Delusions of parasitosis
Diaper rash
Neurotic excoriations
Dermatomegaly (cutis laxa)
Nevus anemicus
Physical allergy
Polymorphous sunlight eruption
Psoriasis with arthritis
Reiter's disease

TABLE 4.—*Proposed Additions (Pathologic)*

Fibrosis, subepidermal
Keratoacanthoma (epithelioma, multiple self-healing)
Kraurosis of penis
Lymphocytoma
Melanosis
Mycosis fungoides
Nevus, blue
Siderosis

TABLE 5.—*Proposed Additions (Etiologic)*

Elastosis, actinic (in place of senile elastosis)
Keratosis, actinic (in place of senile keratosis)
Onychia (toxic-allergic) in addition to infectious)
Porphyria cutanea tarda (in place of epidermolysis bullosa acquisita)

fication in Table 6. Some disorders with double causation are shown in Table 7.

Objections to changes in nomenclature are inevitably raised by authors of textbooks. Having written a few myself, I can sympathize warmly. However, progress is inevitable, and new terms can be used parenthetically in headings until rewriting is feasible.

There are certain diagnoses which have given trouble to the medical student and resident in dermatology. Even though nomenclature is accepted and satisfactory, the diagnoses are used for somewhat different disorders by dermatologists in different countries and sometimes even in the same country. Whether this will ever be changed is problematic. Some disorders in which I have been interested and have written about previously will be discussed briefly.

Dermatitis

One of the most confusing groups of diagnoses for the undergraduate student of Medicine and the resident in dermatology rests upon the designation "dermatitis." The mature dermatologist eventually develops a list of diagnoses in this category which at least satisfies himself, although agreement with the list used by his fellow colleagues is not always close. The ramification of such diagnoses is illustrated by Rabello's list [5] of 24 starting with "dermatitis," which, when added to ten more headed by "dermatite," totals 34. Included therein are eruptions representing epidermal and dermal allergic and toxic reactions, those caused by physical agents, acute and chronic infections, bacterial, viral and fungal, and others of as yet unknown causation.

The description "eczema" has also caused great confusion. Rattner [1] aptly stated: "All eczema is dermatitis, but not all dermatitis is eczema." My library research on Geriatric Dermatoses unearthed a table by Beek [10] which, when interpolated by dividing the percentages of "the eczemas" in different age groups by the percentage of population in that group, a method used by Dr. Carl V. Weller [11] for determining accurately the percentage of incidence of carcinoma and sarcoma at different ages, reveals that "the eczemas" occur with equal frequency throughout life (Table 8). Those of us who have been struggling with patients for many years will possibly agree that the "eczema" of the infant and young child presents a different picture and has a different cause than that of the middle-aged or aged person. The "Standard Nomenclature" presents "eczema" and adds: "Specify allergen when known." This is in agreement with an article by Becker [12] which presented the concept prevalent at

TABLE 6.—*Proposed Changes in Classification*

Acrodermatitis, chronic atrophying (from unknown cause to questionable infection)
Bromhidrosis (from metabolism, growth, or nutrition to infection)
Cutaneous horn (from unknown cause to neoplasms)
Dermatosis papulosa nigra (from unknown cause to neoplasms)
Dermatitis, photomelanctic (berlock dermatitis, from intoxication to physical)
Elephantiasis, nonfilarial (from circulatory to infection)
Nodules, juxta-articular (from unknown cause to infection)

TABLE 7.—*Multiple Causation*

Erythema multiforme (infection, toxic-allergic)
Erythema nodosum (infection, toxic-allergic)
Freckles (congenital, physical)
Intertrigo (infection, physical)
Ulcer, decubital (physical pressure in denervated skin)
Xeroderma pigmentosum (congenital, physical)

TABLE 8.—*Relative Incidence of "Eczemas" Throughout Life (Beek)*[10]

Age	0-20	20-29	30-39	40-49	50-59	60-69	70 & Over
Relative Incidence	0.8	1.1	1.1	1.3	1.1	0.9	1.0

Bloch's Clinic at Zurich that eczema is allergic contact dermatitis. The clinical picture of erythema, edema, gross vesiculation, exudation, and crusting, which can be duplicated by the patch test application of the offending substance, and the characteristic microscopic picture of spongiosis and vesiculation constitute an entity that is easily understood. If it were possible to induce all dermatologists to limit the designation "eczema" to this variety of dermatitis, the medical student and resident would be less confused than they are at present. Many of the dermatoses that are called "eczema" do not qualify in the above-mentioned particulars. Becker and O'Brien [13] found that routine patch tests are valuable in determining the nature and cause of more or less generalized "eczematous" eruptions in adults.

Seborrheic Dermatitis and Seborrheic Eczema

It was stated by Williams [9] in relation to eczema: "But one scrap-basket is enough for the same group and I can see no sense in calling a dermatitis of undetermined origin 'seborrheic dermatitis' just because the patient happens to have a little dandruff. There is a greasy eruption, often ringed, occurring most frequently on the middle of the chest and back which may be called seborrheic dermatitis for want of a better name—it is at least a dermatitis and oily. But why spread the word over a whole group of ill-defined dermatoses?" It is this type of oily dermatitis which has been traditionally called "seborrheic dermatitis" and has been classed in the papulo-squamous eruptions.[14] It occurs only in seborrheic persons and is limited to areas with the largest and most abundant sebaceous glands, namely, the scalp, ears, face, sternal, and interscapular regions. It responds readily to sulfur-salicylic acid ointments. "Seborrheic eczema" is the name given by Unna to a much less definite disorder characterized by involvement of various flexural regions, over which there has been controversy ever since introduction of the diagnosis. At a symposium by Desaux and others,[15] Brocq is quoted as stating that it is not real eczema. Fox [6] stated: "The disease is not true eczema. It may be added that it is not always seborrheic dermatitis." Removal of seborrheic dermatitis from the papulo-squamous group by Pillsbury, Shelley, and Kligman [2] and inclusion under "Dermatitis" does not seem to have simplified the situation. Some British workers and others [16] have discussed the emotional factors in seborrheic dermatitis. It seems possible that some functional dermatides, better designated as "exudative neurodermatitis," have been included.

Dermatitis Medicamentosa

This designation has been used in "Standard Nomenclature of Diseases" for drug eruptions. A term such as Rabello's "Pharmacoderma" [5] might be more appropriate, since drug hypersensitivity produces urticaria, angioneurotic edema, dermatitis, acneform folliculitis, etc. It is convenient to have all eruptions caused by drugs in a single hospital file, in addition, of course, to the files for the particular cutaneous disorders they have caused.

Benign Epidermal Tumors

In 1932, Becker [17] called attention to some discrepancies in pathological nomenclature as regards the skin. While dermal structures (Table 9) form benign neoplasms designated as fibroma, lipoma, chondroma, osteoma, myoma, adenoma, etc., benign neoplasms of the epidermis are rarely, if ever, mentioned. It seems logical to assume that any structure as primitive as the epidermis should form benign tumors. The most prominent candidate for

TABLE 9.—*Benign and Malignant Cutaneous Tumors (Becker)*[16]

Tissue	Benign Neoplasms	Milignant Neoplasms
Fibrous	Fibroma	Fibrosarcoma
Adipose	Lipoma	Liposarcoma
Cartilaginous	Chondroma	Chondrosarcoma
Osseous	Osteoma	Osteosarcoma
Muscular	Myoma	Myosarcoma
Glandular	Adenoma	Adenocarcinoma
Epidermal (epithelial)	?	Epithelioma

this designation is a tumor usually called "seborrheic keratosis" by dermatologists, and "squamous papilloma" by pathologists, which was discussed in detail by Becker.[18] A long list of designations for this lesion is given in the article, to which should be added Lever's "basal-celled papilloma" and Rabello's "nevus senilis."[5] Montgomery[19] also believes that the tumor is a "delayed nevus." It was suggested in 1932[17] that they be called "epithelioma," a designation often used at that time for malignant epidermal tumors. This usage has been gradually discontinued, until now the usual term is "carcinoma." However, since benign epithelial tumors in other parts of the body could also be designated as "epithelioma," it seems feasible to call seborrheic keratosis "epidermoma," since the tumor arises only in the epidermis. "Epidermoma" is given in Dorland's Medical Dictionary as "a cutaneous outgrowth, such as a wart."

Pigmented Nevus

A logical designation for this tumor would be "melanocytoma" or "melanoma," but the use of "melanoma" for malignant melanocytic tumors is well established. The British prefer "benign melanoma" for pigmented nevi and "malignant melanoma" for malignant melanocytic tumors. Pigmented nevus, which Rabello[5] calls "naevus pigmentaris," is so well established and understood that its continuance seems mandatory.

Juvenile Melanoma (Spitz)

Another confusing field is that of atypical pigmented nevi. Miescher[20] directed attention to a form of nevus which he called "fascicular nevus." The melanocytes proliferated in the form of fusiform cells. Helwig called them "spindle cell nevi." In a modified form, they were called "juvenile melanoma" by Spitz.[21] Since they are not malignant, hence not melanomas, a term such as "pseudomelanomatous nevus" might be a more satisfactory designation. While they appear more frequently in childhood, I have seen a section of such a lesion from a man, aged 51, so that "juvenile" may be a misnomer.

Premelanomatous and Early Melanomatous Tumors

A group of diagnoses, the importance of which is of the first magnitude, because of the necessity for life-saving early treatment, prerequisite for which is accurate diagnosis, is given in Table 10. The term that has the greatest use, both by dermatologists and pathologists, is "junction nevus,"[22] which is not quite accurate, since the lesion is not a nevus at all, but rather an obligative premelanomatous or an early melanomatous process. Miescher says they may disappear. My own preference is for Dubreuilh's "lentigo maligna." Rabello[5] prefers "melanosis maligna," which has the same connotation. I have seen several instances of fatality from melanoma because of failure to appreciate the implications of the early lesion. Slow progression, especially of plaques on the cheek,[23] give a false sense of security.

TABLE 10.—*Designations for Lentigo Maligna*

Senile freckle and infective senile freckle	1886 Hutchinson
Lentigo malin des vieillards	1894 Dubreuilh
Lentigo infectieux des vieillards	1895 Bayet
Mélanose circonscrite précancereuse	1912 Dubreuilh
Naevus tardif étalé	1913 Darier
Acquired mole	1920 Hazen
Tardive nevus	1932 Deckner
Dermoepidermal nevus	1932 Allen and Spitz
Melanotic precancerosis	1933 Miescher
Developmental mole	1934 Kumer and Lang
Junction type mole	1941 Traub and Keil
Junction nevus	1947 Sachs et al.
Melanosis maligna	1955 Rabello
Nevoid lentigo	1959 Lund

Melanoma (Malignant)

The various diagnostic designations for melanoma were given by Becker.[24] The recognized diagnosis in the U.S.A. is "melanoma," first suggested by Carswell in 1838. Some dermatologists prefer to designate them as "malignant melanoma." British workers tend to use "benign melanoma" for pigmented (or nonpigmented) nevus and "malignant melanoma" for the malignant tumor. Unna's designation "nevocarcinoma" is still used by some, but, since it is predicated on the supposed derivation of nevus cells from epidermal cells, now practically abandoned, seems to be inaccurate. Malignant tumors of epithelial origin are designated as carcinomas, whether of ectodermal or entodermal derivation. Malignant tumors of mesodermal elements are universally known as "sarcomas." We are not so fortunate in the case of malignant tumors of the nervous system, from which melanocytes originate, since there is as yet no accepted term for malignant tumors. As late as 1931, Stewart and Copeland[25] used the designation "neurosarcoma," which is now practically abandoned, since the tissues are not of mesodermal origin. Dermatologists and pathologists should be familiar with the life history of melanoma, and make recommendations to cancer surgeons for adequate therapy.

Subepidermal Fibrosis vs. Histiocytoma

A group of fairly frequently seen nodules is known under various designations, of which subepidermal fibrosis seems to be the most accurate.[26] Small, repeated hemorrhages introduce lipids and hemoglobin into the tissues, which are ingested by tissue histiocytes, which then contain varying amounts of lipids and hemosiderin. Clinical characteristics may be those of xanthoma and/or hemosiderotic tumors, which have been mistaken for melanoma. They have been called "histiocytomas," Senear and Caro.[27] Pathologists favor the designation "sclerosing hemangioma,"[28] which seems inaccurate for the majority of such lesions, since they have not been preceded by vascular tumors.

There are some discrepancies between the terms preferred by dermatologists and pathologists for, and differences in concept of, some cutaneous tumors. It is anticipated that exchanges of ideas can be arranged with pathologists which could lead to a better understanding of, and mutually acceptable diagnoses for, such disorders.

In conclusion, we have been reminded by Fox[6] ". . . it is realized that nomenclature of disease, like language, is in a constant state of flux and that many more changes will doubtless be made. . . ."

Summary and Conclusions

American literature on dermatologic nomenclature is reviewed.

The "Standard Nomenclature of Diseases and Operations" contains the best available dermatologic nomenclature.

Various groups of dermatoses are discussed, e.g., dermatitis, seborrheic dermatitis vs. seborrheic eczema, dermatitis medicamentosa, benign epidermal tumors, pigmented nevi, juvenile melanoma (Spitz), premelanomatous and melanomatous tumors, and subepidermal fibrosis vs. histiocytoma.

The Committee on Nomenclature of the American Academy of Dermatology and Syphilology has submitted a suggested Nomenclature and Classification to the Board of directors.

It is proposed to collaborate with committees on pathology in an effort to arrive at the best possible designations for various cutaneous tumors.

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ABSTRACT OF DISCUSSION

DR. FRANCESCO RONCHESE, Providence, R.I.: Dr. Becker's excellent presentation gives some good ideas concerning this important problem. Dermatologic nomenclature has improved not only from Alibert's time but also in the last 50 years. We consider now as of more or less historic interest the maze of synonyms, homonyms, and eponyms which has to be sifted if a paper needs a historical foreword. However, one may still complain of lengthy descriptions of slight variations, and of new terms insufficiently explained or justified.

The spirit of specialization may be responsible for the multiplication of names and the creation of hardly justifiable eponyms. Often, the spirit of nationalism enters into the creation of this type of eponyms.

If an international committee agrees on a term, editors of medical publications could help by insisting on its use, particularly in a title. A reasonable number of other terms should be permitted as subtitles. This method would simplify the indexes.

"Malignant erythemato visceritis" is an excellent *subtitle* for "systemic lupus erythematosus," as "angioreticulomatosis" for "Kaposi's sarcoma" and "mast cell disease" for "urticaria pigmentosa." "Basalioma" and "melanomalignoma" are interesting single-word terms.

Our patients with keratoses will be pleased with the use of the term "actinic" in place of "senile." I agree with Dr. Becker that "maculae cerulae" is an invisible entity. I prefer not to have "cutis hyperelastica" as synonym of "Ehlers-Danlos syndrome." This is an example demonstrating that in selected cases, the eponym, making a three-word title, is preferable to an incomplete synonym or to a lengthy description containing all the components of a syndrome.

As Dr. Becker and the committee on nomenclature point out, whenever possible, English should

be used in place of Latin and Greek. I like to add French and German, too. The English language is spoken today by such a large majority of the world's population, and so little Latin and Greek is taught in our schools that, whenever possible, the main title of a paper should be in English. The prevalence of the English language today is shown by the extensive summaries in English, by the periodicals dedicated only to reviews in English, and by entire medical journals that are printed in English in non-English speaking countries. The use of English in place of Latin and Greek will help to reduce the eye-sore of grammatical errors. Linear scleroderma will give the same clinical impression as *en coup de sabre;* excoriated acne will be a shorter term—will include both sexes and will sound less sophisticated than *acné excoriée des jeunes filles.* I do not see any particular reason to say *peau d'orange, en plaques, d'emblée* and *grattage* when one can say just as effectively orange skin, in patches, primary, and scratching.

DR. ROY L. KILE, Cincinnati: It is most discouraging to try to straighten out something as difficult as this problem of nomenclature. However, I do not think it is completely hopeless.

For years we have had committees on nomenclature in various dermatological organizations and to the best of my knowledge little has been done. This committee of the American Academy of Dermatology is going to at least try!

As soon as changes are suggested, I find that the average dermatologist riles up and tries to defend and protect the term that he wants to use. Fortunately for the Committee, through the efforts of Dr. Rattner, we were able to have accepted some of our recommendations for the "Standard Nomenclature of Disease" of the American Medical Association. This, as you all know, is now accepted and used in all the record rooms of accredited hospitals throughout the United States. For this reason, there will be some weight borne by the recommendations of the Committee.

I beg of you to secure your indulgence and cooperation if we suggest changes that do not entirely agree with your thinking. It is going to be hard. It is hard for all of us to make changes. Actually, I have heard men suggest changes in terminology and then a few minutes later use the term they suggest we not use.

The complications of usage are so difficult that it almost seems hopeless. However, if you all will help by cooperating with us, in trying your best to teach and use the terms recommended, it certainly will make the problem much easier. True, no one should be dictatorial in the use of terms. Physicians are such individualists they strongly resent this. In the interest of teaching and to try to simplify I believe this is one place we must put aside some of this feeling in order to accomplish a worthwhile objective.

Even if only a little is accomplished it will be worthwhile. The problem is such a complex one and so little has been done.

DR. A. ROSTENBERG JR., Chicago: I rise because I think the record should be clear about one of the points that Dr. Becker made, with which, if I understood him correctly, I certainly am not in agreement; namely, that the patch test or any other kind of test can enable us to arrive at a diagnosis, that is, a morphological diagnosis. The patch test or any other test is, of course, of extreme value in arriving at an etiological diagnosis, but our first duty, especially as dermatologists, is to make a correct morphological diagnosis, and then, if indicated, proceed with various etiologic procedures, including patch tests. This is the great error that the general practitioner and nondermatologist makes. Being uncertain of the morphologic diagnosis, they wistfully but naively hope that if they only do enough tests the morphologic diagnosis will be revealed. What difference does it make if a man gives a history of exposure to poison ivy, if he is patch-test-positive to poison ivy, and if he has an eruption that is on the exposed areas, if it happens to be scabies? The ability to make a morphologic diagnosis is what distinguishes the dermatologist, not that I for a moment claim that the dermatologist can always make a morphologic diagnosis, but I think it is incumbent upon us to bring home to the medical profession that there is no substitute for the morphologic diagnosis.

DR. ARTHUR R. WOODBURNE, Denver: In the new list that Dr. Becker has recommended, there was one term that I think should be altered before it gets in. I refer to "polymorphous sunlight eruption." We know that this is not necessarily due to sun. Other sources of light produce polymorphous light eruption as well.

DR. NORMAN N. EPSTEIN, San Francisco: I should like to emphasize the point that Dr. Ronchese made that when a term is approved internationally, it should be one that is used.

I recently had the pleasure of attending the Iberian Dermatological Congress. Naturally, I could not speak Portuguese nor read it, but at the demonstration of clinical cases, it was surprising how often I was able to interpret the presenting diagnosis on the history sheet. If we adopt a general change in nomenclature, I think, we should take into consideration that we often travel to foreign countries, and eventually an international classification will have to be adopted.

DR. ERVIN EPSTEIN, Oakland, Calif.: I realize that the committee has considered all the problems concerned with nomenclature. However, I should like to ask Dr. Becker how they can substitute the term "Reiter's disease" for "keratosis blennorrhagica." Not only are they not the same disease, etiologically, but Reiter's disease is not even a skin disease. Only a small percentage of patients

with Reiter's disease have cutaneous lesions at all, and, of those who have dermatologic manifestations, only a very small proportion present the dermatosis that we call "keratosis blennorrhagica."

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: To standardize nomenclature carries implications that pertain to one's credo, the convictions by which one lives.

Dr. Becker's slides illustrate the particulate or discrete structure of science, which resembles a line spectrum with individual components analogous to individual views. It is not a continuous spectrum, and it requires a sort of quantum mechanics for its interpretation.

To standardize means, inescapably, to trim to a preconceived pattern, to bend and prune and abridge and restrain and constrain, to chisel from the freedoms of thought and of speech and of the press, and so to violate elemental principles of science and democracy.

Dr. C. T. Onions, editor of the "Oxford English Dictionary," lists words people have used, defines them, and dates them as to when they entered the language and when they died out. H. W. Fowler, author of "The King's English," describes how to use words effectively and in good taste. Neither lexicographer nor grammarian preempts an attitude of, "Thou shalt" or, "Thou shalt not."

To accommodate learned committees on hospital records with rubber-stamp interpretations and to accommodate bad statisticians with bad statistics, we are asked to acquiesce to restricted and specified arrangements of sounds and alphabetical symbols! Stand aside and look at two things: yourself, and words; which will you have as master and which as servant?

To standardize is to set in a habitual routine, to delimit range, to bar windows, to bow before a stiff propriety that obsolesces as it is born, to accept the beaten path because it is beaten.

Standardization offers an advantage of sorts; there is opium in it. An approved cataloging of a case exhilarates with the illusion of achievement, lulls with the delusion of adequacy, fortifies with the folklore magic in a name, drugs with an anesthesia of curiosity. You know as well as I that to diagnose "psoriasis" benumbs the instinct of a hunter and reduces to a complacent purveyor of tar a man with the birthright, if not the ability, of Ehrlich, Pasteur, Harvey, Vesalius.

You have my willing ear. I give you unlimited leave to ply me with persuasion. You are welcome to my shirt if you need it more than I do. But you may not circumscribe my universe of mental activity.

When these hardworking gentlemen of the Committee indicate that standardizing nomenclature involves hard problems, I am glad. I hope the problems remain insurmountable forever.

DR. HERMANN PINKUS, Monroe, Mich.: Dr. Sutton has said many things I wanted to say. Concerning nomenclature I am a heretic, and I like to sound a warning against making it too rigid and standardized. We have to keep in mind for what purpose we make the nomenclature. If you talk about a standard nomenclature of diseases for the use of librarians and hospital file clerks, that is one thing. It should be simple and uniform. The same considerations apply to medical students.

When we begin to teach residents, however, I think it is much better not to have dermatological nomenclature too standardized. For instance, if you do not teach a young dermatologist that parapsoriasis guttata is also pityriasis lichenoides chronica, he loses something because one term relates the disease to the didactically useful concept of parapsoriasis, the other one to pityriasis lichenoides acuta et varioliformis. It sets a student's mental activities moving if he has to consider different aspects of one disease and informs him about the historical development of dermatologic concepts. Variety in terminology also helps us to express our individual views more precisely, and it would be awful if there was no disagreement!

The question of Reiter's disease interests me. I agree with Dr. Epstein that Reiter's disease is not the same as keratosis blennorrhagica, which I believe can still be caused by gonorrhea. But it intrigued me to hear that here an eponymic term is introduced into the standard nomenclature. I am happy about it, because I think some eponyms, such as Darier's disease, are better terms than any of the synonyms that have been proposed. In other instances I would plead for retaining and perhaps increasing the number of dermatological names that mean nothing in particular, such as syphilis or psoriasis or histiocytosis X, which are just given names by which we know the disease. These terms do not impute etiological or other theories which might be changed ten years later. On the other hand, such misleading terms as adenoma sebaceum for Pringle's disease and eosinophilic granuloma for anything from granuloma faciale to histiocytosis X, lymphoblastomas, and insect bites should be eliminated speedily but seem to lead a hallowed life. The "Standard Nomenclature of Diseases and Operations," I understand, is meant for cross-filing purposes in hospitals and other institutions mainly. It should be stable and simple and there seems no particular objection against anglicising it. But let us not force this fixed terminology on the thinking minds of dermatologists. Scientific intercourse requires a terminology that is flexible, diversified, and internationally intelligible.

DR. HARRY L. ARNOLD JR., Honolulu, Hawaii: I think we are inclined to forget that this is only part of a much larger problem, that is, the growth of language in general. We might well be warned by what has happened to the French language over the years by the sharp restrictions of it by the French Academy, permitting only those words to be added of which the Academy approved. This has never happened in English, and it is one of English's most valuable features, that it does change, that it is flexible, that it is every man's right to write it in his own way and to make new words if he wants too. It is more true of "American," of course, than of English.

I should, with all due respect to Dr. Sutton, for all my agreement with what he said, remind him of the famous literary figure who exemplified the *reductio ad absurdum* of this view, when he said that he used words exactly as he pleased, that he and not the word was the master, and that he always paid the word a little extra if it meant a little extra work. He used the word "impenetrability" to mean, "There's a nice knockdown argument for you." I am referring to Humpty Dumpty.

DR. MARION B. SULZBERGER, New York: I do not want to prolong this discussion, but I feel that I must say something at this time.

First of all, I want to express my condolences to these two committees. Having been chairman of the Committee on Nomenclature of the last International Congress of Dermatology, and having had the duty to appoint a new International Committee on Nomenclature, this matter has been of some concern to me and to many of our colleagues on this Committee of the International Congress. We all worked very hard, notably Professor Rabello of Brazil and Professor Hermanns of Holland, but we came up with nothing, because of the impossibility of coming to agreements, because each and every system which was proposed was objected to strenuously by some one or other of the Committee.

I agree entirely with what Dr. Arnold just said and with what others have said, that nomenclature is just a part of language, and you cannot make language change by decree. It is not possible. There is a question of usage and adaptability and elasticity, and language is usually formed by forces which men do not deliberately and consciously create or obey by edict. That is always going to be more or less the case also with medical nomenclature, I am now convinced.

I should like to say, though, I do not see how we could agree to many of the changes in nomenclature as Dr. Becker showed. Just for instance, I do not understand his-statement that he has never seen maculae cerulae. This just passes my understanding. Are not they the same thing as tâche bleuâtre? Didn't we see them almost every day? I do not understand that. There must be areas in the world where this is still pediculosis pubis and where there are still maculae caerulae.

That brings me to the second point. I cannot understand how we can take the attitude that any nomenclature we in America now decide upon or try to adopt or recommend should be anything less than international in its applicability. The purpose is to make ourselves understood throughout the world, the great shrinking world. One of the great advantages of medicine and the medical sciences is that we are largely equipped with international languages. We must maintain these. Any term which is designed to be used only locally and with only insular applications, any term whose understanding is localized and confined to one country or language zone is today completely inadequate.

DR. HERMAN BEERMAN, Philadelphia: I rise only to say that as a member of two committees, Dr. Rattner's and Dr. Becker's, I can attest to the amount of work that these two gentlemen have put into this effort.

Secondly, I believe that there have been good examples given here this morning of exactly what we are trying to avoid—the verbiage of some persons who should be directed to simplify their presentations.

DR. S. WILLIAM BECKER, Long Beach, Calif. (Closing): I greatly appreciate all the discussion. In reply to Dr. Rostenberg, it has been my experience that patients who present folliculoporal patch tests do not show the typical vesicular patch tests which have been interpreted as so-called epidermal allergy. They do, however, show positive reactions to proteins applied by the scratch or intradermal techniques. Additional studies along this line may furnish further information about them. In reply to Dr. Ronchese and Dr. Sulzberger, we all agree that nomenclature should be international. Not much progress has been made to date, but it is anticipated that the Nomenclature and Classification Committees of the XIIth International Congress will be of great assistance along this line.

Goeckerman Therapy in the Management of Common Dermatoses

HAROLD N. COLE Jr., M.D., Cleveland

The use of crude coal tar as a useful adjunct in the treatment of cutaneous disease was first reported by Fischel [1] in 1894. One of its earliest staunch proponents in this country was C. J. White,[2] who found it to be of great value in a wide variety of conditions.

However, to the present day, the exact manner in which tar acts upon the diseased skin is unknown. In animal experimentation tar is known to produce epidermal proliferation, and yet dermatologically tars are employed to reduce hyperkeratosis, parakeratosis, and acanthosis. Rothman and Shapiro [3] would explain this seeming discrepancy by the fact that tar initially has a suppressing action on the rete pegs and dermal papillae.

Coal tar has long been recognized as causing sensitization of the skin to ultraviolet rays. Goeckerman [4] originally used this principle with excellent results in psoriasis. This sensitizing effect of coal tar is apparently due to acridine compounds in the anthracene oil fraction.

Fleischauer [5] in 1930 showed that the photosensitizing effect of coal tar is greater when the tar has been completely removed from the skin prior to ultraviolet irradiation than when a thin film is allowed to remain, as originally recommended by Goeckerman. The photosensitization reaction was shown to occur as early as fifteen minutes after the application of tar, and to last for as long as seventy-two hours. Obermayer [6] concurred in the opinion that the photosensitization effect induced by crude coal tar lasted for more than twenty-four hours, and that, therefore, it was not necessary to leave a film of tar on lesions during exposure to ultraviolet light.

An important advance in overcoming the criticisms to the use of crude coal tar, both from the standpoint of esthetic and practical considerations, was first reported by Combes [7] who obtained excellent results with the use of Zetar, in which the source of raw material is anthracite, the temperature range of distillation between 650 C. and 750 C., with the retort horizontal in position. The tar obtained by this process is very uniform and, in addition, during the course of manufacture is micronized, thus making it readily miscible with and soluble in water.

Sullivan [8] gave a pertinent review of the use of actinotherapy for a wide variety of dermatoses and suggested a renewed effort to evaluate properly its true effectiveness.

With this view in mind, and the desire to find a modality of therapy other than x-ray, which might be of value particularly in common chronic recalcitrant dermatoses, the following study was carried out using a modified form of Goeckerman therapy.

Methods

The source of ultraviolet irradiation employed was a standard Hanovia hot quartz ultraviolet lamp emitting wave lengths between 2,400-3,660 A. units with an axial average output at 30″ of 1,000μw. per sq. cm. of skin surface.

The source of crude coal tar used was Zetar because of its advantages of complete

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TABLE—*Goeckerman Therapy for Office Use*

Condition	No. Cases	Best Response with Goeckerman	No Better Response than Other Therapy
Psoriasis	188	178	10
Recalcitrant pustular eruptions	42	30	12
Nummular eczema	44	38	6
Seborrheic dermatitis	90	88	2
Atopic dermatitis	134	90	44
Neurodermatitis (localized)	26	24	2
Psoriatic keratoderma	24	24	—
Chronic infectious dermatitis	96	62	34
Pustular psoriasis	24	24	—
Folliculitis decalvans	2	1	1
Dyshidrosis	36	30	6
Pseudo-pelade	2	—	2
Keratoderma (tinea)	12	12	—
Keratoderma climactericum	4	4	—
Congenital ichthyosiform erythroderma	2	2	—
Granuloma annulare	4	4	—
Total	730	610	120

miscibility and solubility in water and because of its relative uniformity in chemical composition.

Patients were instructed to take a tar bath daily using the tar emulsion, 2 tablespoons (30 cc.) to the bath.

Where conditions of the scalp existed, patients were instructed to employ tar shampoo two to three times weekly.

Where it was found to be practicable, tar incorporated in lotions, creams, or ointments was employed nightly.

All patients were given a suberythema dose of ultraviolet at regular intervals of not more than two weeks.

Results

All patients in whom this modified Goeckerman regimen was employed were treated in the routine of a private office practice. Admittedly, it would be impossible to run a scientifically ideal control series in such a purely clinical study. However, an impartial attempt was made to compare the end-results of this treatment with a control case of the same condition, of approximately the same degree of involvement and severity, treated with other modalities of therapy, including x-ray in some.

Comment

In the beginning, varying time schedules for ultraviolet therapy, twice weekly, once weekly, etc., were used. Finally, however, the schedule of a treatment every two weeks was arrived at, as office visits oftener than this were considered impractical for the average person. Thus, the practicality, as well as the efficacy of such comparatively infrequent treatments, remained to be determined.

Intentionally, no mention is made in regard to total span of time over which treatments were given. Obviously, the majority of conditions under consideration are of a chronic, recurrent nature.

Naturally, the question would arise as to the possibility that in the Goeckerman-treated series the response might have been due to tar therapy alone. However, a large number of patients in the control series were treated with tar therapy alone, and definitely did not show the same degree of favorable response exhibited by those who also received ultraviolet therapy.

Of the 730 patients treated, twelve either initially or ultimately showed definite sensitivity to coal tar.

Of the 16 different dermatoses or variants thereof included in this study, 10 are common conditions with which the dermatologist is ordinarily confronted in everyday practice (psoriasis, recalcitrant pustular eruptions, nummular eczema, seborrheic dermatitis, atopic dermatitis, neurodermatitis, psoriatic keratoderma, chronic infectious dermatitis, pustular psoriasis, and dyshidrosis).

It is true that the majority of patients treated are included in the categories of

psoriasis, seborrheic dermatitis, and atopic dermatitis, which have been previously reported as responding well to the Goeckerman regimen. It is gratifying, however, to find that such entities as neurodermatitis, chronic infectious dermatitis, nummular eczema, recalcitrant pustular eruptions, keratodermas, and even granuloma annulare, appear to be so favorably influenced by this modality.

The action of either coal tar or ultraviolet on the abnormal skin is still largely a matter of conjecture. Patients subjected to either one alone definitely failed to show the response afforded those who received the combined effect. It would seem that, in addition to the mere photosensitization effect, there is probably a symbiotic physiochemical action in the skin produced when both are employed in conjunction.

Summary

A simple practical form of modified Goeckerman therapy for routine office use is presented.

This study would indicate that this is an extremely useful adjunct to the treatment of many common dermatoses in addition to psoriasis, and that it is of particular value in the management of a variety of chronic recalcitrant dermatoses which are notoriously unresponsive to other measures, including x-ray.

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ABSTRACT OF DISCUSSION

Dr. Frank C. Combes, New York: It is really stimulating to listen to a paper supporting a therapeutic method introduced years ago by a clinician of considerable repute. Sometimes I think we are all bent on attaining the new, but not sufficiently concerned or interested in utilizing what we already possess. As Dr. Cole has said, physical therapy of this type is free of the dangers associated with radiation of a more penetrating quality, and, there is, in addition, no cumulative effect. However, there are certain factors with which all who use the Goeckerman method should be familiar.

First, we must appreciate that the effects of crude coal tar and ultraviolet radiation (in certain specific spectral bands) are keratoplastic. The fluorescent green or anthracene oil fraction in the former is the most active. Ultraviolet radiation acts by suppressing the overactivity of the malpighian layer of the epidermis.

The mechanism of this photodynamic action has been explained on the basis of absorption of the photosensitizing fraction by the cells of the malpighian layer, where it becomes intimately associated with oxidizable substances in the cell. It is activated by capture of a quantum of radiant energy of a specific wave length, and reacts with O_2 with resulting damage in the cell structure. As a consequence, there is a deficiency of oxygen and a retardation of the process of keratinization.

The effects of the combined use of crude coal tar and ultraviolet radiation in therapy may be either additive or synergistic. The latter is due to the photosensitizing effect of components of the coal tar. Topical photosensitization is an interesting phenomenon, the cause of which is obscure, although we are familiar with a few of the prerequisites, namely: 1. the photosensitizing substance (in this case, coal tar) must be capable of penetrating to the malpighian layer and be in contact with the skin for a length of time sufficient to do this.

2. The wave length which is applied to the area in order to demonstrate or accomplish this phenomenon must be of that quality which is absorbed by the specific photosensitizer. It is entirely independent of those wave lengths capable of causing sunburn, and the attendant erythema is not related to sunburn; in fact, the photosensitizer may actually lessen sunburn effects.

3. The reaction is more intense if all trace of the photosensitizer is removed from the surface of the skin; in fact, any residual coal tar will have

a depressing effect and will lessen the sensitizing effects of the radiation.

We now come to the photosensitizing properties of coal tar. These vary, and understandably so. First, crude coal tar, in the general pharmaceutical market, is usually not crude. About fifteen years ago, I made a careful study of coal tars from all over Europe and the North American continent. The coal and gas industry in the United States is not interested in marketing crude coal tar for medical purposes. There is no money in it. Coal tar is distilled for commercial fractions, especially naphthalenes, acridines, and phenols. What is left is used for roofing, insulation, wood preserving, road building, and small amounts for medicinal purposes. You see, therefore, that the photosensitizing fraction would vary greatly.

The principal photosensitizing ingredients of coal tar with their corresponding spectral absorption bands are anthracene and acridine and occur predominantly at 3,200 and 3,800 A. units with a narrow absorption band at 2,500 A. Phenanthrene is absorbed further in the ultraviolet range and has narrower absorption bands at approximately 2,200 and 2,800 A. 1,2-benzpyrene, an important fraction of anthracene oil, has spectral bands at 2,544 and 3,640 A.

Dr. Cole has used a lamp emitting wave lengths varying between 2,400 and 3,660 A. He would, therefore, get photosensitization from Zetar, which is a real crude coal tar. However, one must appreciate that lamps vary greatly in the quality of their spectrum emission and the quartz bulb deteriorates rapidly due to age, intense heat (1,000 C), handling, and improper cleaning. Even under ideal conditions, it can devitrify, developing crystals of crysobalite and trydmite. Both of these differ from fused quartz in their emission spectra.

At the Skin and Cancer Unit in New York, many years ago, one of the ultraviolet burners was actually coated with tiny crystals because the nurse carefully washed it every day with rubbing alcohol. No ultraviolet went through, but patients did remarkably well. In fact, a male patient was forgotten and left under the lamp during lunch time, from noon until two o'clock, and he did not have any ultraviolet erythema, only mild redness from the heat.

I wish to thank Dr. Cole for the privilege of opening the discussion on his paper. His method is timely, useful, and effective. It is useful not only in psoriasis, but in any dermatosis in which we wish to induce a keratoplastic or reducing action.

DR. MARCUS R. CARO, Chicago: I am a little concerned about the value of controls used in the evaluation of a method of treatment for diseases as capricious as psoriasis. It has been my experience that no two patients with psoriasis are entirely the same in their response to treatment or their lack of response to it.

I should like to suggest a rather simple method of control. In the case of pustular psoriasis of the hands, it should be possible to have the patient immerse one hand in the coal tar solution and then to expose both hands equally to the ultraviolet light. In generalized eruptions of psoriasis, the patient can fill the tub half full and then lie on his side, immersing only one half of the body, either the right or the left, in the tar bath and then expose the entire body to the ultraviolet light. In this way, each patient will serve as his own control for the effectiveness of the treatment being used.

DR. FRANK E. CORMIA, New York: I should like to congratulate Dr. Cole on this very excellent presentation. I have been particularly interested in this type of treatment in nummular eczema.

As you know, many patients nowadays do not like x-ray therapy, and there are a good number of patients who do not respond to local antibiotics, plus hydrocortisone. About a year or so ago, I had a patient with an extremely recalcitrant nummular eczema. He was not a very cooperative patient. I had planned to see him every five to seven days, but, instead of that, he would wander in about every two weeks. I was giving him Zetone ointment, then for some reason or other, I decided to give him ultraviolet light. He did beautifully. After two treatments, the nummular eczema was gone. This has, therefore, been a standard routine in my office since that time.

DR. HAROLD N. COLE JR., Cleveland, (Closing): Dr. Caro has a very legitimate objection to the lack of perfectly controlled conditions in the control series of a purely clinical study of this sort. It is virtually impossible.

The control group was simply observed as carefully and impartially as practical considerations would allow.

The New, Newer, and Newest

Names in the News

—Among the group of distinguished physicians honored by Northwestern University Sept. 29 on the occasion of its Centennial Celebration of the founding of the Medical School were Arthur Stillians and Tom Sternberg. The proceedings were impressive with representatives present from almost every medical school in the country. Dr. Stillians, Professor Emeritus in Dermatology, received a Distinguished Service Award and Dr. Sternberg, an alumnus, a Merit Award for his substantial contributions to the Continuing Education Program of the U.C.L.A. School of Medicine and to dermatology.

—Walter Lever has been appointed to a four-year term on the Study Section for General Medicine of the National Institutes of Health succeeding Marion Sulzberger, whose term has expired.

—Anthony Cipollaro received the annual Gold Medal Award from the Italian-American Charitable Society, Inc. of Boston for "notable contributions by an American of Italian ancestry to the progress, defense, and welfare of the Nation"—the first time that a physician has been honored by the Society.

—Sidney Olansky has been appointed Professor and Chairman of the Department of Dermatology at Emery University School of Medicine.

—Jan Schwarz, Director of the Laboratory of Mycology in the Department of Dermatology, University of Cincinnati, was honored at a dinner by his former students and co-workers on the occation of his fiftieth birthday, Sept. 13, 1959. Dr. Schwarz is Assistant Professor in both Dermatology and Pathology.

—"Fletch" Hall is now Clinical Professor of Dermatology at the U.S.C.

—John Belisario has been elected a Fellow of the Royal Australasian College of Physicians, the only dermatologist to be so elected since the College was founded. In addition, The Royal Prince Alfred Hospital has established the John Belisario Institute of Dermatology, a two-story building on the hospital grounds, named for Belisario at the request of the members of the dermatological staff.

—H. A. Dixon of Toronto was elected Canadian President of the Section of Dermatology at the Canadian Medical Association Meeting in Edinburgh, Scotland, last July. The British Medical Association was host for the occasion which attracted an attendance of more than 2,000 physicians.

—Yutaka Mishima has the honor of being the first physician in Japan to receive a Ph.D. degree in dermatology.

New Administrations

—*The New England Dermatological Society*
Joseph Goodman, President, Paul J. Catinella, Vice-President, Robert F. Tilley, Secretary.

—*Los Angeles Dermatological Society*
Jerome K. Fisher, President, Gordon MacDonald, Secretary.

—*Dermatology Section, Connecticut State Medical Society*
Louis E. Garston, President, Frank Gastiglione, Secretary.

—*Baltimore Dermatological Society*
Francis Ellis, President, Israel Zeligman, Vice-President, Stanley N. Yaffe, Secretary.

—*Detroit Dermatological Society*
Alice F. Palmer, President, Clarence Livingood, President-Elect, John N. Grekin, Secretary, Robert E. Burns, Recorder.

Miscellany

—H. C. Goldberg of Plainfield, N.J., addressed the American Podiatry Association Aug. 31, on the "Laboratory Evaluation of Fungus Growths in Shoes, Socks, and Skin" for which he was awarded a silver medal and $200 for research in podiatry.

And a happy holiday to all of you!

H. R.

Correspondence

EPIDERMAL CHANGES ASSOCIATED WITH SCLEROSING HEMANGIOMAS

To the Editor:—Seven years ago I presented before the Pacific Dermatologic Association a paper on "Diagnostic Pitfalls of Dermal Pathology" (*A.M.A. Arch. Dermat. & Syph.* 67:18, 1953), in which I catalogued all of the errors I had made or had barely avoided making in many years of work in dermatohistopathology. The recent paper by Dr. H. J. Halpryn and Dr. A. C. Allen on "Epidermal Changes Associated with Sclerosing Hemangiomas" A.M.A. ARCH. DERMAT. 80:160, 1959) exemplifies one of the dangers against which I cautioned, namely, a complete dependence upon a histopathologic impression without a concomitant thorough examination of the gross lesion or a study of its clinical course.

The lesions under discussion have been interpreted variously and designated as histiocytoma, sclerosing hemangioma, dermatofibroma lenticulare, fibroma durum, and nodular subepidermal fibrosis. In their paper based upon a histopathologic study of sections from 114 lesions obtained from 102 patients, the authors report that "basal-cell carcinomas were found in nine cases (or 8% of all lesions examined). . . . Several varieties of seborrheic keratosis were seen in 13 cases (or 11% of all lesions studied)."

The paucity of information obtained by the authors about these cases is demonstrated by their statement that "preoperative clinical diagnoses were available in only 50 (44%) of the 114 lesions reviewed. In most cases designations such as 'lesion,' 'growth,' 'nevus,' or 'cyst' were used. In no instance did the submitting physician use the term 'dermatofibroma' or one of its synonyms; and in no case was any notation made about surface changes above the lesion." And yet on the basis of the sections alone the authors have placed on permanent record a statement of their conclusion that 8% of the histiocytoma lesions they examined developed an overlying basal-cell carcinoma. This report poses a frightening prospect for the countless possessors of these ubiquitous cutaneous lesions.

In our paper on "Histiocytoma Cutis" (*Arch. Dermat. & Syph.* 33:209, 1936) Dr. Senear and I discussed the clinical and histopathologic features and the pathogenesis of these lesions, and we stated that "the benign character of the histiocytoma has been emphasized by all observers." During the intervening 23 years hardly a day has gone by without bringing to my attention at least one of these common and inoffensive lesions. I cannot recall ever having seen a histiocytoma that became ulcerated or invasive or that showed any clinical changes that might have suggested a malignant supervention. Nor have I ever seen a lesion diagnosed as carcinoma grossly that on section showed the features of a histocytoma in the underlying corium.

In our paper on "Seborrheic and Senile Keratoses" (*M. Clin. North America*, 35:419, 1951) Dr. Szymanski and I discussed the clinical and histopathologic features of seborrheic keratoses. I cannot recall ever having seen a histiocytoma that grossly assumed features that simulated those of a seborrheic keratosis. In the innumerable specimens I sectioned that were diagnosed clinically as representing seborrheic keratosis I have never seen the histopathologic features of a histiocytoma in the underlying corium.

In my paper on "Diagnostic Pitfalls of Dermal Pathology" I stated that in histiocytoma cutis "occasionally one finds a pseudoepitheliomatous basal-cell hyperplasia that may simulate a superficial basal-cell epithelioma." This histopathologic finding, I repeat, is not synonymous with the diagnosis of cancer.

I also stated then, and, evidently it bears repeating, that ". . . . histopathologic study alone cannot lead to the correct final diagnosis. In each instance all the clinical features must be ascertained and then added to whatever information may be obtained through the use of the microscope before a final appraisal of the case is made. To attain the highest level of diagnostic skill in dermatology one should study each patient with eyes that are disciplined by a knowledge of the pathologic processes that may be present; one should examine each histopathologic section with a vision that is ripened by clinical experience."

Marcus R. Caro, M.D.
25 E. Washington St.
Chicago 2.

REPLY TO DR. MARCUS R. CARO

To the Editor:—It would seem reasonably clear that the way effectively to dispute or confirm the conclusions of the study by Dr. Halpryn and me is not by tendentious pronouncements but by a dispassionate systematic analysis of a corresponding sample. However, even prior to such an analysis, if Dr. Caro chooses to call a lesion of the type depicted in Figure 5 of our paper a simulated rather than a genuine basal-cell carcinoma, then the source of his disagreement becomes clear. The main point of the paper, which apparently has not been thoroughly appreciated, is that a dermal tumor—a sclerosing angioma—may induce hyperplastic and neoplastic changes. Herein is a basic pathogenetic phenomenon that deserves further exploration.

Arthur C. Allen, M.D.

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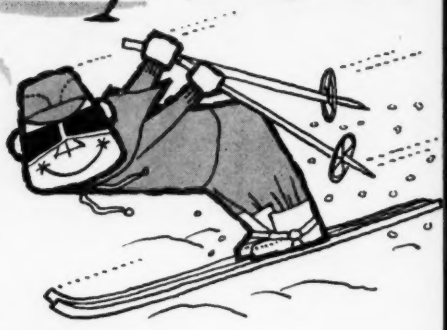

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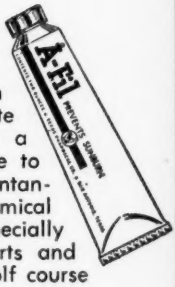

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moisturizes and softens the skin

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supplements natural skin oils

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Pruritus senilis—pruritus hiemalis
In nummular dermatitis
In psoriasis
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erences: 1. Bleiberg, J.: J. M. Soc. New Jersey *53*:371, 1956. 2. Clyman, S. G.: tgrad Med. *21*:309, 1957. 3. Welsh, A. L. and Ede, M.: Ohio State M. J. *50*:837, 4. 4. Abrams, B. P. and Shaw, C.: Clin. Med. *3*:839, 1956. 5. Welsh, A. L. and , M.: J.A.M.A. *166*:158, 1958. 6. Welsh, A. L. and Ede, M.: Ohio State M. J. 805, 1959. 7. Clyman, S. G.: Ind. Med. & Surg., *27*:531, 1958.

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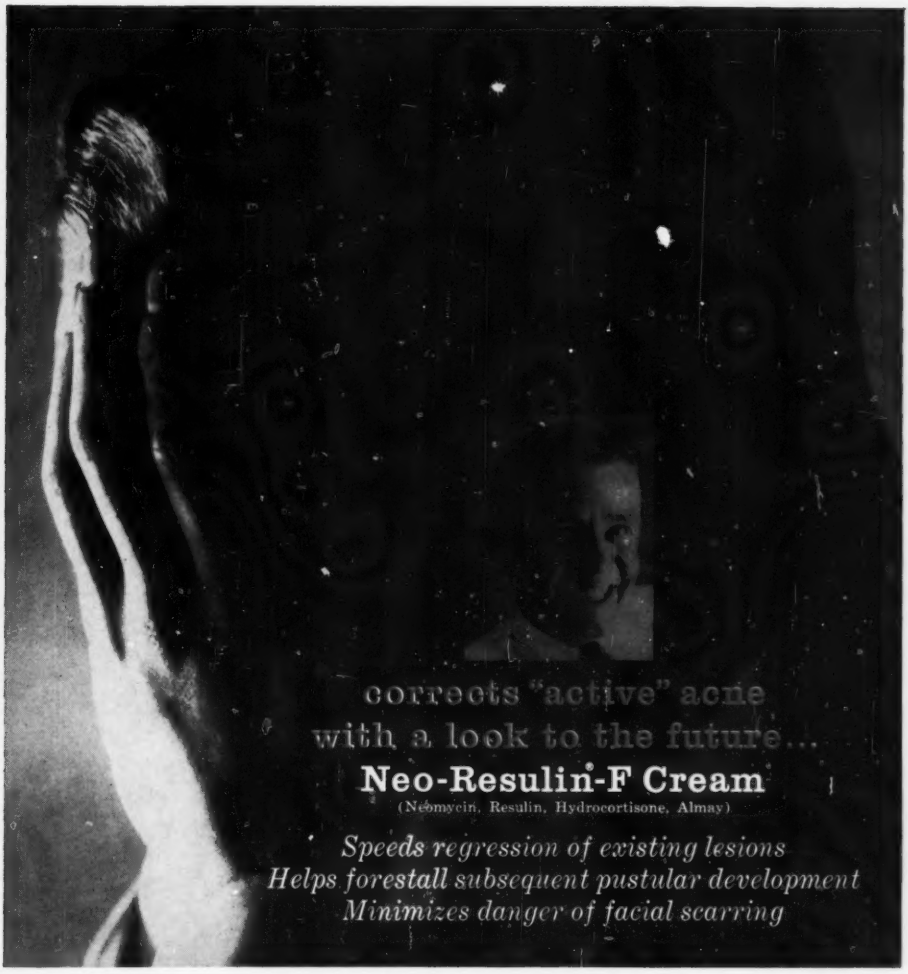
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(Neomycin, Resulin, Hydrocortisone, Almay)
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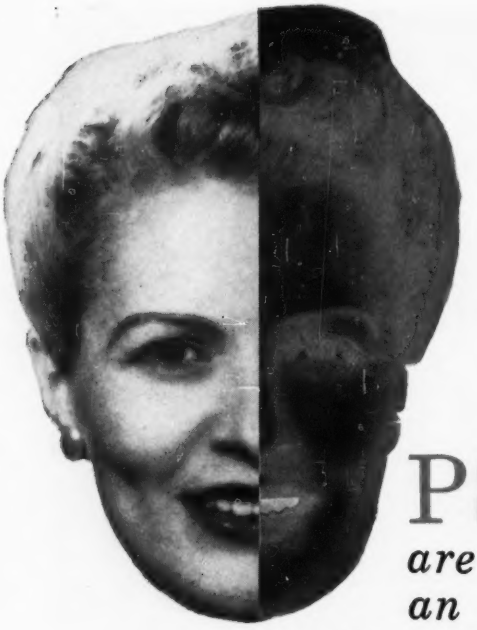

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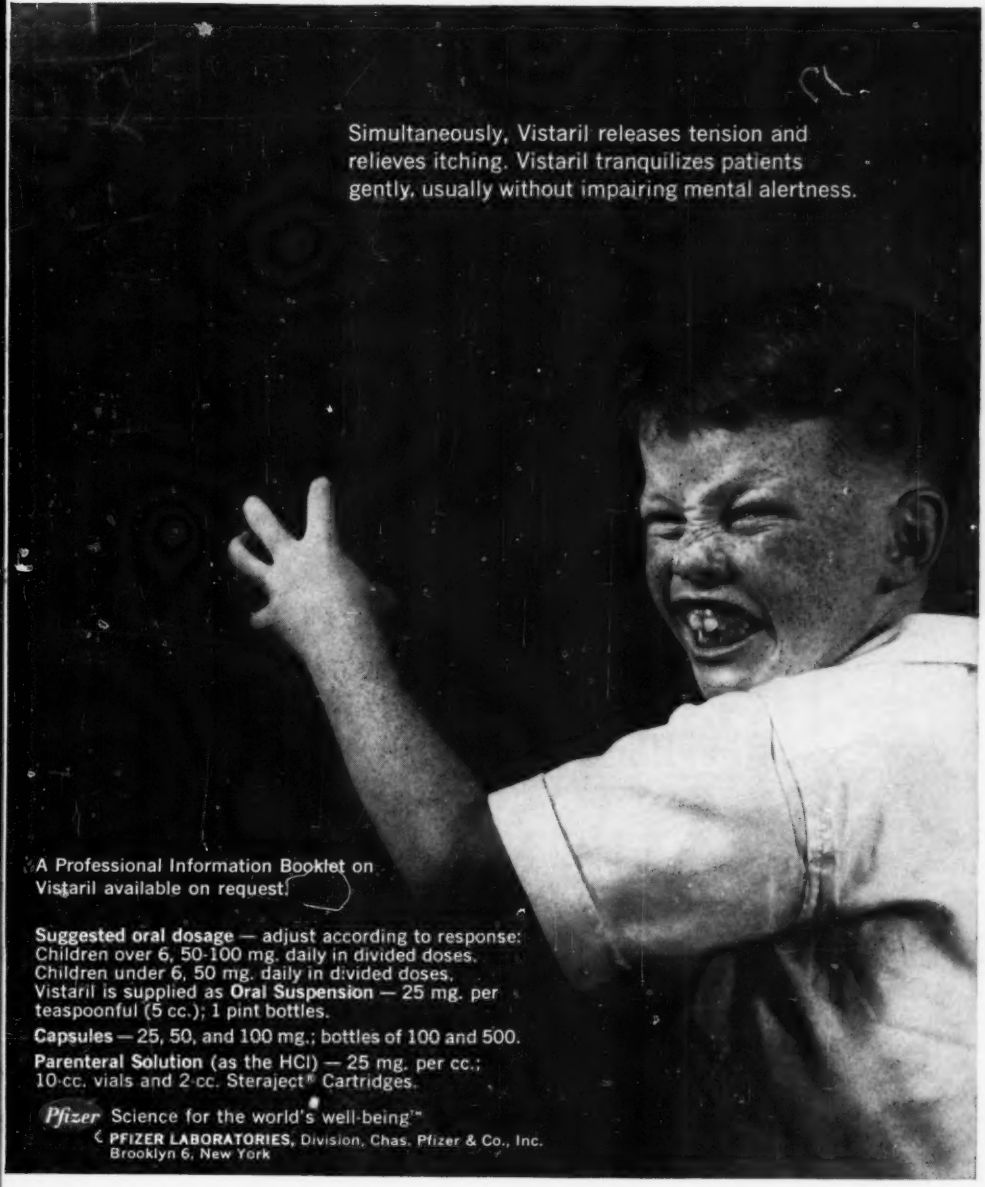

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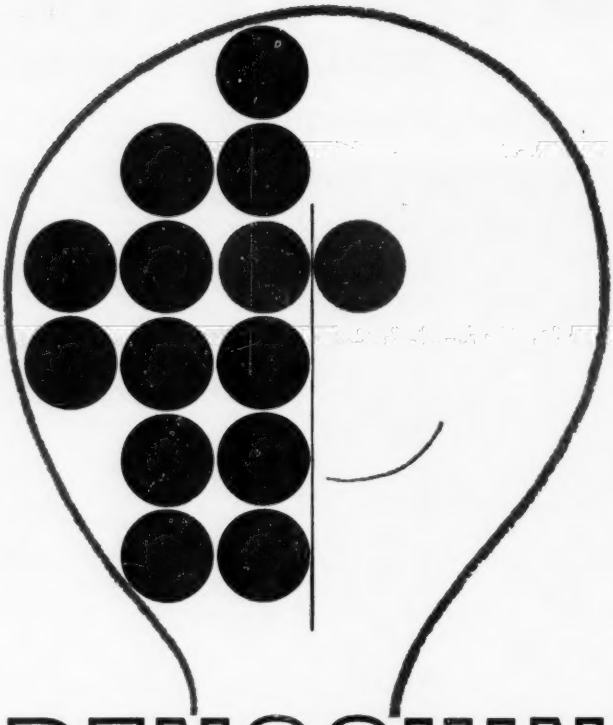

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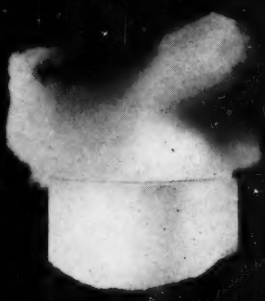

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1. Frank, L.: Research Report 1.35

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1. Shaw J. M., and Crowe, F. W.: Skin Protective Ointments. Arch. Dermat. & Syph. 71: 379, 1955.

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IN ALUMINUM ACETATE VEHICLE

COR-TAR-QUIN is especially effective in those dermatoses where an inflammatory reaction is accompanied by increased scaling, lichenification, and secondary infection.

Combined hydrocortisone-coal tar therapy produces an enhanced antipruritic, anti-inflammatory response and diiodohydroxyquinoline is fungicidal as well as bactericidal. The Acid Mantle creme base of COR-TAR-QUIN helps restore and maintain normal pH of the skin. Relief is prompt and lasting.

Sig: Apply b.i.d. ½ oz., 2 oz., and 4 oz. tubes with either 0.5% or 1.0% hydrocortisone

INCORPORATED IN EXCLUSIVE ACID MANTLE VEHICLE

also available without the stainless tar, as CORT-QUIN™ CREME pH 4.5

A MOST TRUSTED NAME IN DERMATOLOGICALS

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in "burns, ulcers and sloughing wounds... successful"*

*In "burns, ulcers and sloughing wounds...a decrease in purulent material, cleaner granulation tissue and an increased rate of epithelization...[PANAFIL] proved to be a successful chemical débriding agent ...no effect on viable tissue, and the complications were relatively few in number and were never serious."
Katz, R. I.; Reese, J. W., and Byrne, J. J.: Am. J. Surg. 95:102, 1958.

panafil® topical enzyme therapy

Rystan
Mount Vernon, N.Y.

- effective wound cleansing and healing
- well tolerated and convenient for outpatient use
- economical for hospital and patient

PANAFIL ointment (papain – urea – water-soluble chlorophyll derivatives) • For complete information see your Physicians' Desk Reference
33489

Pleasingly and efficiently
serving patient and physician
during all seasons

SUPERFATTED

BASIS® SOAP

For dry sensitive skin

Available at Prescription Pharmacies

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Mfrs. of Aquaphor®—Elastoplast®

BASIC
IN ANY SUCCESSFUL ACNE PROGRAM:
SCRUPULOUS CLEANSING OF THE SKIN

ACNE-DOME®

CLEANSER pH 4.2
U.S. Pat. No. 2,876,164

medicated cleansing cream for skin and scalp in acne

multiple action—thorough but gentle

- restores normal skin acidity to aid healing, prevent further infection
- produces a sea of suds . . . without harsh soaps or detergents
- leaves skin clean and dry . . . but not too dry
- maintains optimal skin-peeling . . . just enough to help remove comedones

Contains bithionol 1%, sulfur 2%, salicylic acid 2% and Colloidal-Soy-Bean-Fraction in the exclusive ACID MANTLE® (buffered aluminum acetate) vehicle.
Supply: 4-ounce jars.

* A cellulose sponge accompanies each jar for more complete, more effective application of ACNE-DOME Cleanser.

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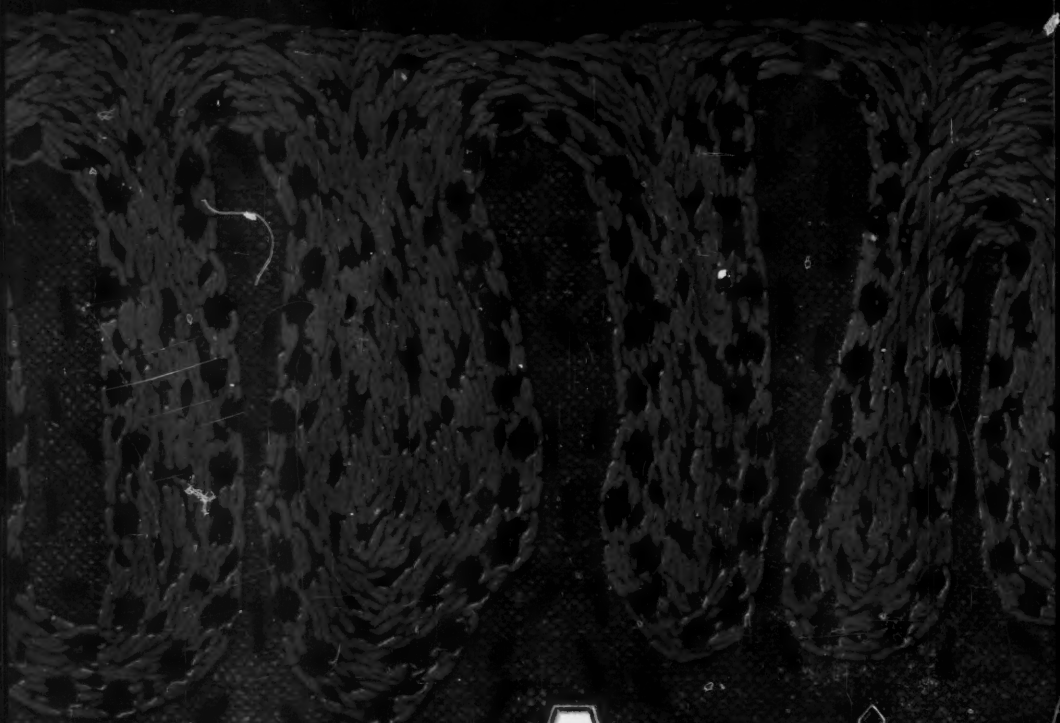
Los Angeles / Montreal • *World Leader in Dermatologicals*

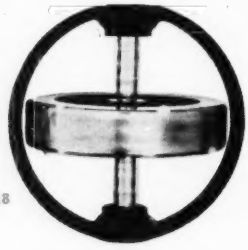
in allergic and inflammatory skin disorders including psoriasis



unsurpassed for total corticosteroid benefits

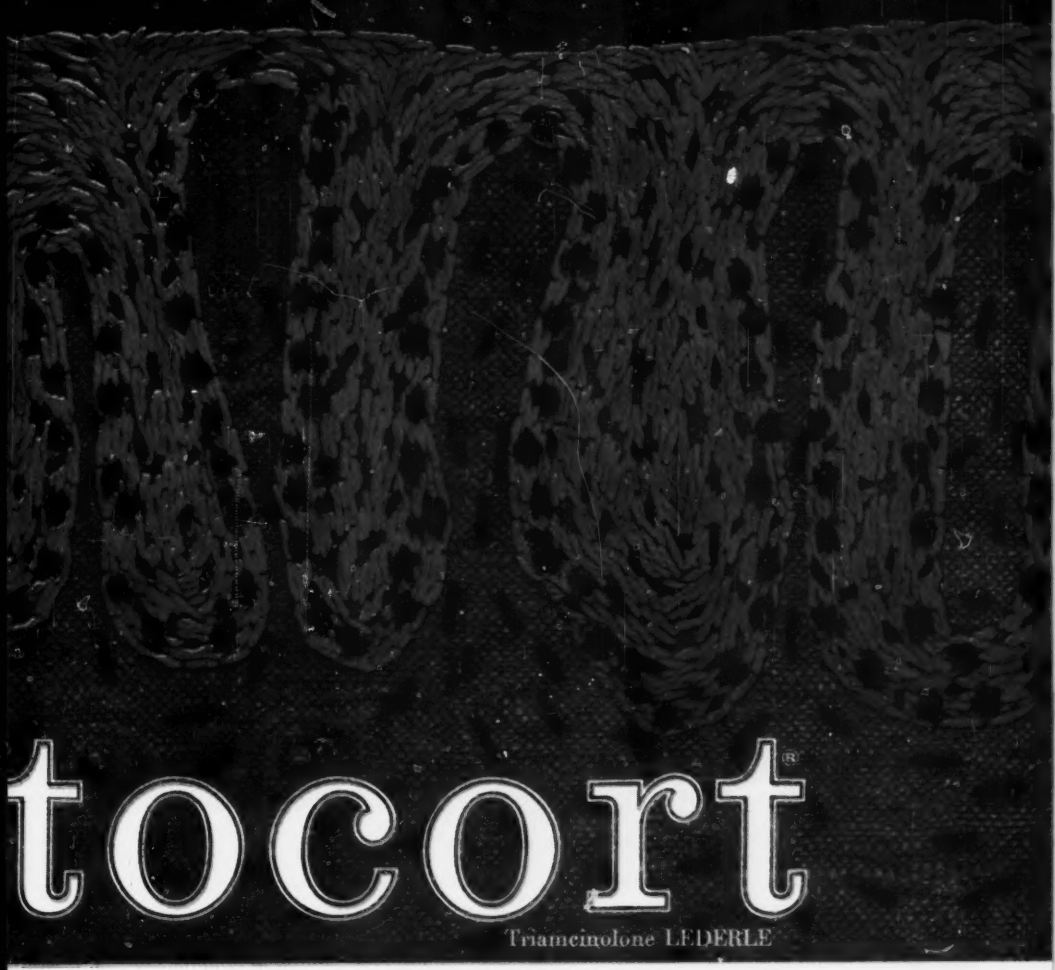
Aris

Substantiated by published reports of leading clinicians



- **effective control** of allergic and inflammatory symptoms[1-3,7,8,12-15,17,18]

- **minimal disturbance** of the patient's chemical and psychic balance[1,4-18]



At the recommended antiallergic and anti-inflammatory dosage levels, ARISTOCORT means:

- **freedom from salt and water retention**
- **virtual freedom from potassium depletion**
- **negligible calcium depletion**
- **euphoria and depression rare**
- **no voracious appetite— no excessive weight gain**
- **low incidence of peptic ulcer**
- **low incidence of osteoporosis with compression fracture**

Precautions: With ARISTOCORT all traditional precautions to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress symptoms.

After patients have been on steroids for prolonged periods, discontinuance must be carried out gradually over a period of as much as several weeks.

Supplied: 1 mg. scored tablets (yellow); 2 mg. scored tablets (pink); 4 mg. scored tablets (white); 16 mg. scored tablets (white).

Diacetate Parenteral (for intra-articular and intrasynovial injection). Vials of 5 cc. (25 mg./cc.).

List of References 1-18 supplied on request.

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*"Twenty-two cases of chronically infected wounds and ulcers were treated with...[PANAFIL]. In 18 cases, very marked and rapid improvement in the appearance of the wounds occurred. Excessive necrotic and cellular debris was effectively removed and there was early appearance of healthy granulation tissue." Carpenter, E. B.: Virginia M. Month. 85:22, 1958.

in"...infected wounds and ulcers...rapid improvement"*

panafil® topical enzyme therapy

Rystan
Mount Vernon, N.Y.

- effective wound cleansing and healing
- economical for hospital and patient
- well tolerated and convenient for outpatient use

PANAFIL ointment (papain – urea – water-soluble chlorophyll derivatives) • For complete information see your Physicians' Desk Reference

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SHEPARD'S
Cream Lotion

Contains sufficient sesame oil to lubricate without excess grease

Not occlusive

No lanolin or lanolin derivatives

Available unscented as well as scented

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- effective against most "...pathogenic cocci regardless of their resistance to antibiotics,"[4] including even strains of staphylococcal phage group 80/81.[4]

- "...effective in secondarily infected eczematoid eruptions, ulcers or epidermophytosis infected with saprophytic coagulase negative staphylococci and Pseudomonas and Proteus vulgaris."[5]

- "...patients in whom *in vitro* studies demonstrated penicillin resistance responded rapidly to...[Triburon]."[6]

- "In view of the increasing number of antibiotic-resistant strains...[Triburon] merits consideration in many dermatological conditions."[5]

For effective control of skin

well-tolerated · nonstaining

active even against antibiotic-resistant pathogens

References:

1. E. Edelson, E. Grunberg and T. V. Morton, *Antibiotics Annual 1958-1959*, New York, Medical Encyclopedia, Inc., 1959, p. 110.
2. R. C. V. Robinson and L. E. Harmon, *Antibiotics Annual 1958-1959*, New York, Medical Encyclopedia, Inc., 1959, p. 113.
3. Reports on file, Roche Laboratories.
4. R. J. Schnitzer, E. Grunberg and W. F. DeLorenzo, *Antibiotics & Chemother.*, 9:267, 1959.
5. F. T. Becker and J. L. Tuura, *Ann. New York Acad. Sc.*, 82:(1), 131-134, Sept. 1959.
6. P. L. Williams, *ibid.*, pp. 135-140.

Triburon
treatment
in skin
disorders

whether acute

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J. L.—age 8. Atopic dermatitis with secondary pyoderma of 2 weeks' duration.

After Triburon-HC Ointment t.i.d. for 12 days.

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NEW Triburon-HC OINTMENT (WITH HYDROCORTISONE)

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not an antibiotic • not a sulfonamide • not a nitrofuran

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for prevention and treatment of dermatologic disorders when the anti-inflammatory and antipruritic action of a steroid is desirable, such as:

- pruritus
- eczema
- ecthyma
- carbuncles
- hydradenitis

Available: Ointment, containing 0.1% Triburon plus 0.5% hydrocortisone, in 5-Gm and 20-Gm tubes.

Triburon

for prevention and treatment of dermatologic disorders such as:

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- pyodermas
- furunculosis
- infected dermatoses
- pustular folliculitis

(Triburon-impregnated dressings can be autoclaved.)

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normal protective cover

Normal skin has an acid pH range between 4 and 6

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Supply:
ACID MANTLE Creme: 1 oz. tubes, 4 oz. & 16 oz. jars.
ACID MANTLE Lotion: 1 oz. and 4 oz. squeeze bottles, 1 pint bottles.

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CREME or LOTION pH 4.2

In housewives' eczema and industrial dermatitis, promptly restores and maintains the normal protective acidity of the skin. Active ingredient is aluminum acetate in specially formulated bases.

"The importance of a measure designed to return the pH of the skin quickly to its normal values after exposure to soap and alkalies is amply borne out..."

—Gross, P., et al.: A. M. A. Arch. Dermat. & Syph. 70:94,1954

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No Moisture * Send For Details

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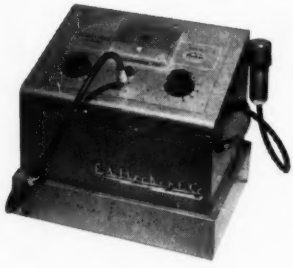

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When your patient suffers from histamine-induced skin reaction

Whether caused by drugs, dander, or detergents, most histamine-induced skin reactions (such as the sulfonamide reaction shown above) respond rapidly to 'Teldrin' *Spansule* capsule therapy.

Just one capsule in the morning, another at night, provides 24-hour antihistamine effect. And because of the prolonged, even release of 'Teldrin' medication, side effects are minimal.

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brand of chlorprophenpyridamine

brand of sustained release capsules

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topical strategy. .

ACHROMYCIN OINTMENT 3%

For infectious dermatoses. Unsurpassed broad-spectrum control of causative organisms and complicating mixed invaders. Excellent local toleration; low sensitizing potential. In ½ oz. and 1-oz. tubes.

ACHROMYCIN OINTMENT 3%
WITH HYDROCORTISONE 2%

For inflammatory dermatoses. Classic corticoid suppression of erythema, swelling, weeping, pruritus plus ACHROMYCIN control of pyogenic or subclinical secondary infection. In 5 Gm. tube.

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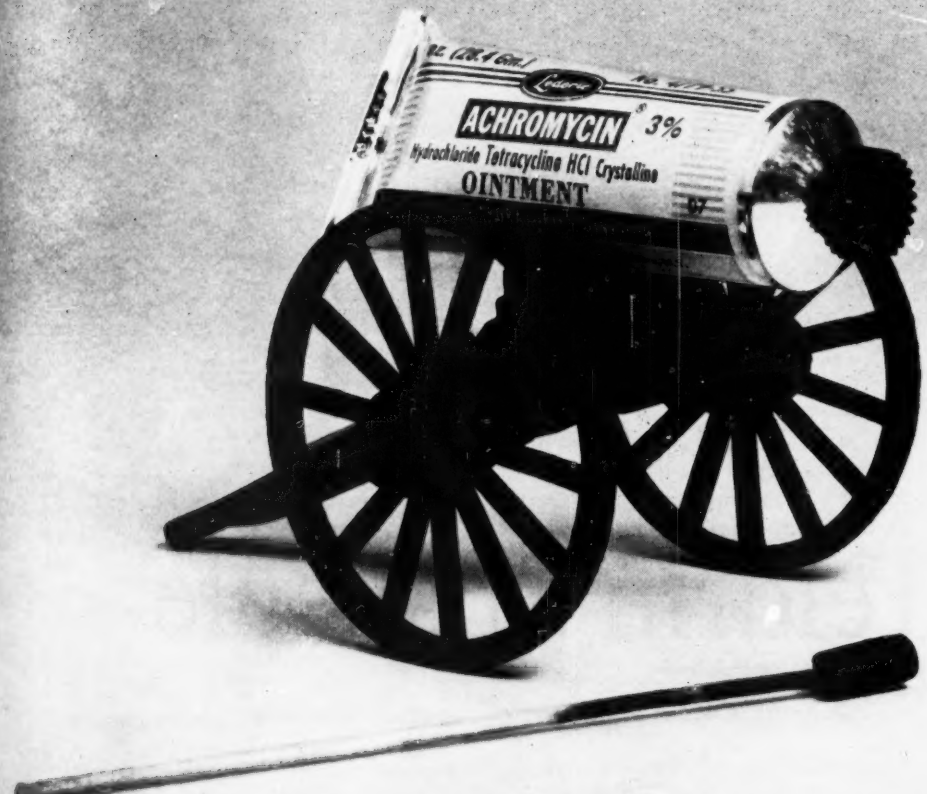
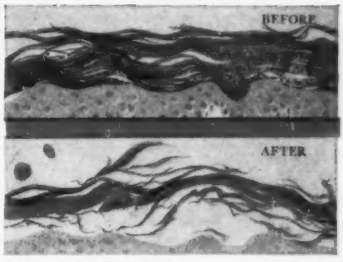


LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

New freedom from embarrassment and distress of psoriasis!

Alphosyl®

LOTION

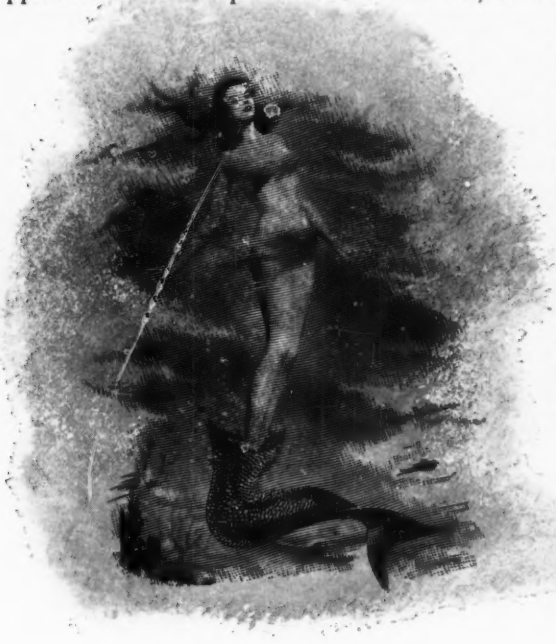


DISAGGREGATES PSORIATIC SCALE

In vitro studies show that the keratin-dispersing action of allantoin is exceptionally effective in disaggregating psoriatic scale.[1,2] It apparently acts on an abnormal cement substance between cornified cells.[2,3] Coal tar, too, helps break up the horny layer.[2] Together, these agents provide rapid clearing of psoriatic lesions as well as the underlying inflammation and erythema.

ALPHOSYL Lotion, used by many physicians both in routine practice and in carefully controlled studies, proved highly successful.[2,4-7] The lotion permits complete avoidance of the potential hazards of certain other methods of treatment, such as superficial x-ray, heavy metals and corticosteroids.[7]

Advantages: • Treatment-fastness not observed • Cosmetic qualities permit free application to the scalp • Well tolerated • May be freely used on tender areas



FORMULA: Allantoin 2% and special coal tar extract 5% in a greaseless, stainless, vanishing lotion base.

SUPPLIED: Bottles of 8 fl. oz.

APPLICATION: For maximum therapeutic results rub thoroughly into lesions 2 to 4 times daily. For maintenance apply once or twice a week.

REFERENCES: 1. Flesch, P.: Proceedings Scientific Session. Toilet Goods Assoc. June, 1958. 2. Samitz, M. H.: Ann. New York Acad. Sc. 73:1020, 1958. 3. Flesch, P., and Jackson Esoda, E. C.: Ann. New York Acad. Sc. 73:989, 1958. 4. Bleiberg, J., and Saltzman, J. A.: Clin. Med. 5:485, 1958. 5. Bleiberg, J.: Ann. New York Acad. Sc.: 73:1028, 1958. 6. Clyman, S. G.: Ann. New York Acad. Sc. 73:1032, 1958. 7. Welsh, A. L., and Ede, M.: Ohio M. J.: to be published.

For psoriasis with acute inflammation

Alphosyl-HC®

Alphosyl with 0.25% hydrocortisone
Supplied in bottles of 4 fl. oz.

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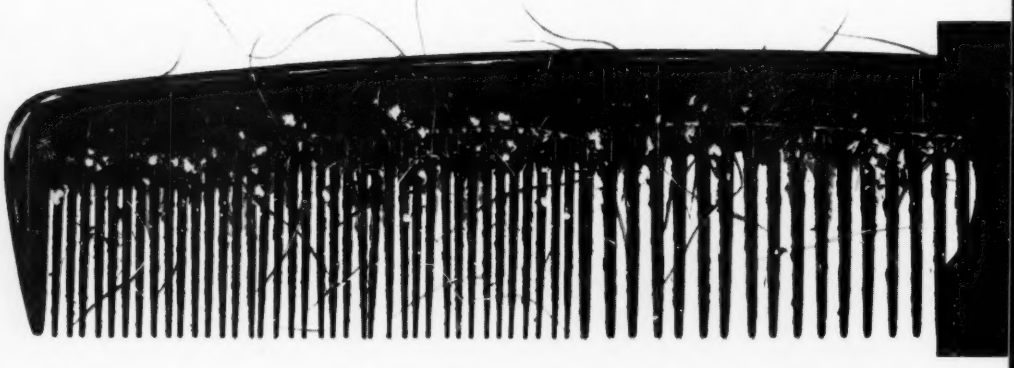
doctor,

you wouldn't have
such a comb...

(yet some of your patients do)



PHYSICIANS SAY:

- *safety*—"No toxic side effects were seen."[1] " . . . increased oiliness, loss of hair and staining . . . were not noted."[2]

- *effectiveness*—"Of eighty-four patients . . . seventy-nine [94%] obtained good to excellent results."[3]

THEIR PATIENTS SAY:

- *cosmetically acceptable and easy-to-use*—"This product is remarkably well accepted by the patients as an excellent, foamy shampoo, free from any objectionable odor . . ."[4]

Capsebon is available on prescription only.

References: 1. Harvey, J. H., and Ereaux, L. P.: Clinical study of cadmium sulfide shampoo, Canad. M.A.J. *79*:917 (Dec. 1) 1958. 2. Stough, D. B.; Lewis, R. A.; Farmer, B. L.; Osment, L. S., and Noojin, R. O.: New beneficial agents in the treatment of acne vulgaris and seborrheic dermatitis, Postgrad. Med. *24*:439 (Oct.) 1958. 3. Kirby, W. L.: Preliminary and short report: Cadmium sulfide shampoo in seborrhea capitis, J. Invest. Dermat. *29*:159 (Sept.) 1957. 4. Mullins, J. F., and Barnett, J. R.; Cadmium shampoo treatment of seborrheic dermatitis, Texas J. Med. *53*:640 (Aug.) 1957.

. . . they'll appreciate **Capsebon**™

1% CADMIUM SULFIDE SUSPENSION

a dandruff treatment that isn't a "waste of time"

to control dandruff with Capsebon

1. The patient should thoroughly shampoo with Capsebon or his usual cosmetic shampoo.
2. After rinsing, shampoo with Capsebon, working up a rich lather. Allow the lather to remain on hair and scalp for *at least* 5 to 10 minutes.
3. Rinse thoroughly.

Supplied: In 4-ounce plastic bottles.

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Borcherdt's

MALT SOUP EXTRACT

(MALTSUPEX)

POWDER

shows good results. We would like to send you the recently published paper by Dr. Louis H. Brooks who says,

"It was found that administration of Malt Soup Extract in dosages of one or two tablespoonfuls twice daily produced favorable results. Within two or three days after beginning this simple regimen, the itching and burning usually disappeared. Frequently there was prompt remission of symptoms which was followed by improvement in the condition of the tissue of the anal canal and the perianal skin.*

Malt Soup Extract promotes the growth of aciduric flora in the lower tract. Because this product is a food and not a drug, there are no side effects. Because it is not habit forming, it can be given over long periods of time when necessary. Diabetic patients should allow for 60 calories for each tablespoonful.

Malt Soup Extract Powder is specially processed non-diastatic barley malt extract neutralized with potassium carbonate.

Two heaping tablespoonfuls twice a day is the usual effective dose and this may be reduced to two tablespoonfuls at bed time when satisfactory results are secured.

Malt Soup Extract is available in liquid and powder form in 8 oz. and 16 oz. jars at most drug stores coast to coast.

*Diseases of the Colon & Rectum, Vol. 1, No. 5, Sept.-Oct. 1958.

Samples and literature gladly sent on your request

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NEW 4" x 10 YD.

Non-Ravelling

DOME-PASTE® BANDAGE

DOME

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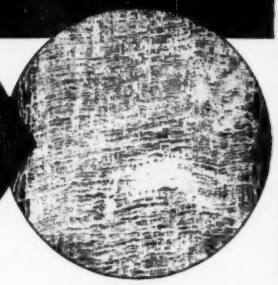

Frayed edges, uneven impregnation, difficult to apply.

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Thread-locked edges, firmly woven; medicament spreads uniformly, easy to apply.

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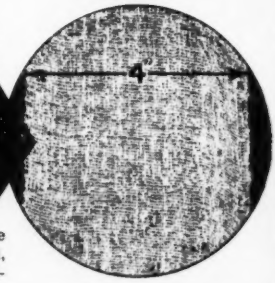

The new Dome-Paste bandage is flesh colored, 4" x 10 yd. gauze bandage... impregnated with glycerine, zinc oxide, gelatine paste.

RECOMMENDED

for leg ulcers resulting from thrombophlebitis (particularly the post partum and post-operative kinds), stasis edema and chronic venous insufficiency associated with varicose veins, and varicose eczema, lymphatic edema and thrombophlebitis of the superficial saphenous vessels.

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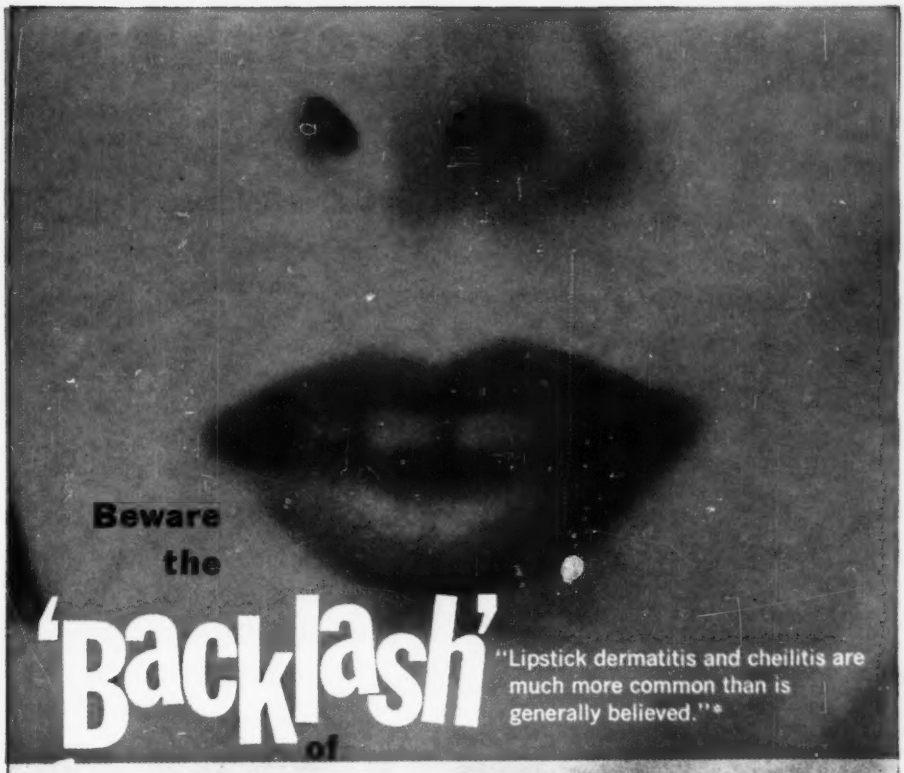

Dermatoses resulting from sensitivity to a variety of lipstick ingredients can be avoided by using MARCELLE Lipsticks — another reason to remember and suggest MARCELLE® HYPOALLERGENIC COSMETICS for the patient with a cosmetic allergy or sensitivity.

MARCELLE Lipsticks — available in a full range of colors — are offered in different formulas to eliminate common sensitizers, and to avoid perfumes and the bromofluoresceins. The MARCELLE Lipstick Testing Kit, providing 14 different formulations, enables you to help your patient select a lipstick best suited to her case.

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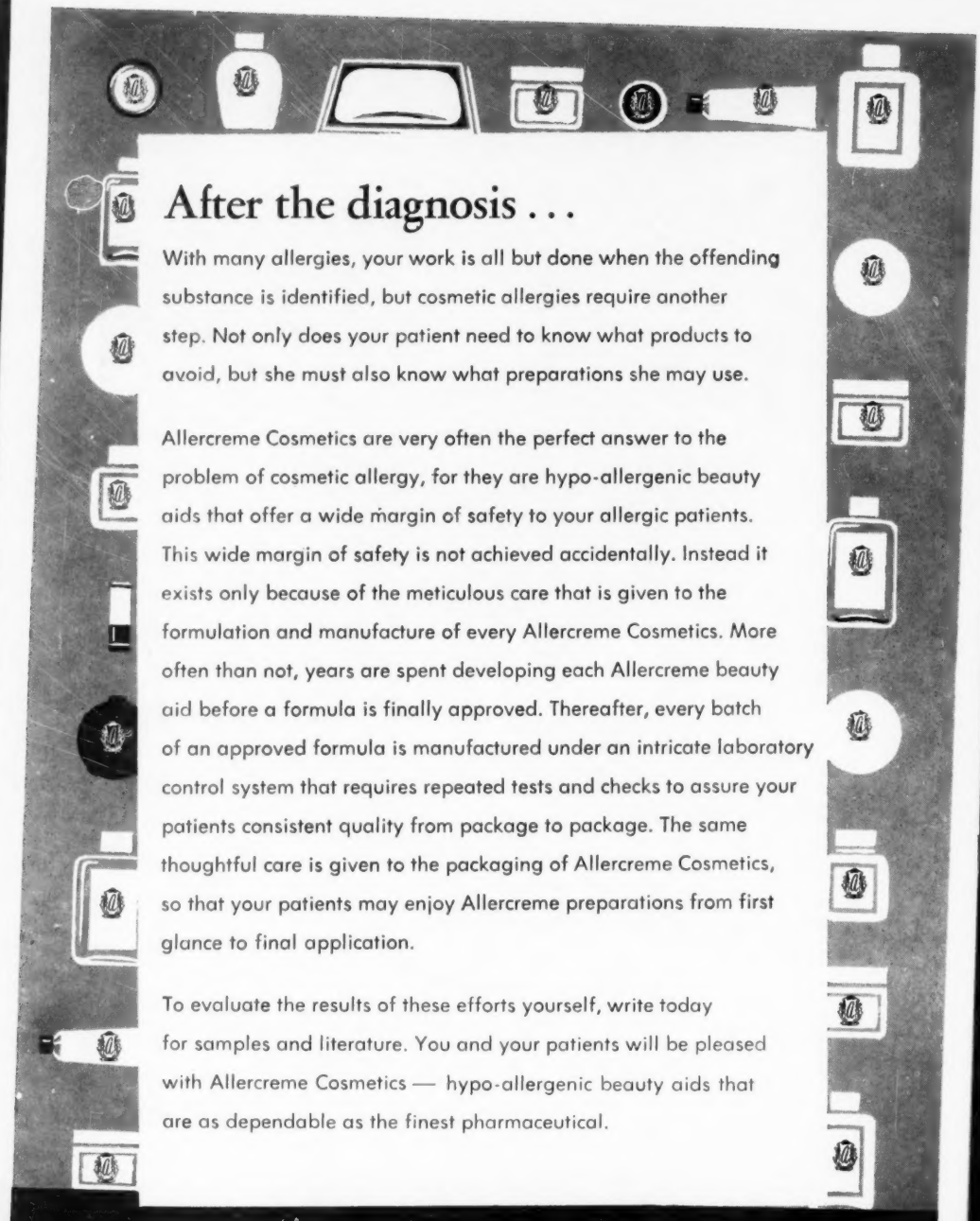
*Zakon, S. J., et al.: Arch. Dermat. & Syph. 56:499, 1947; abstracted in Birmingham, D. J., and Campbell, P. C., Jr.: Occupational and Related Dermatoses, U. S. Public Health Service Publication No. 364, 1954.



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With many allergies, your work is all but done when the offending substance is identified, but cosmetic allergies require another step. Not only does your patient need to know what products to avoid, but she must also know what preparations she may use.

Allercreme Cosmetics are very often the perfect answer to the problem of cosmetic allergy, for they are hypo-allergenic beauty aids that offer a wide margin of safety to your allergic patients. This wide margin of safety is not achieved accidentally. Instead it exists only because of the meticulous care that is given to the formulation and manufacture of every Allercreme Cosmetics. More often than not, years are spent developing each Allercreme beauty aid before a formula is finally approved. Thereafter, every batch of an approved formula is manufactured under an intricate laboratory control system that requires repeated tests and checks to assure your patients consistent quality from package to package. The same thoughtful care is given to the packaging of Allercreme Cosmetics, so that your patients may enjoy Allercreme preparations from first glance to final application.

To evaluate the results of these efforts yourself, write today for samples and literature. You and your patients will be pleased with Allercreme Cosmetics — hypo-allergenic beauty aids that are as dependable as the finest pharmaceutical.

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Soothing Olive Oil Bath Additive

Permits Pruritus Patients to Bathe in Comfort

TRIDENOL is a thoroughly effective, clinically desirable, mildly scented, new, soothing, preparation for addition to the bath. For the relief of patients who suffer from dry skin, and who experience itching and burning after bathing.

TRIDENOL, when added to the bath, leaves a thin film of pure olive oil on the skin. This acts as a soothing agent for irritated, itching and sensitive skin, and prevents loss of moisture.

TRIDENOL is highly purified imported olive oil, made dispersible in hard or soft water by means of a non-irritating, non-ionic, surfactant, octylphenoxyethanol.

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Professional samples available on request.

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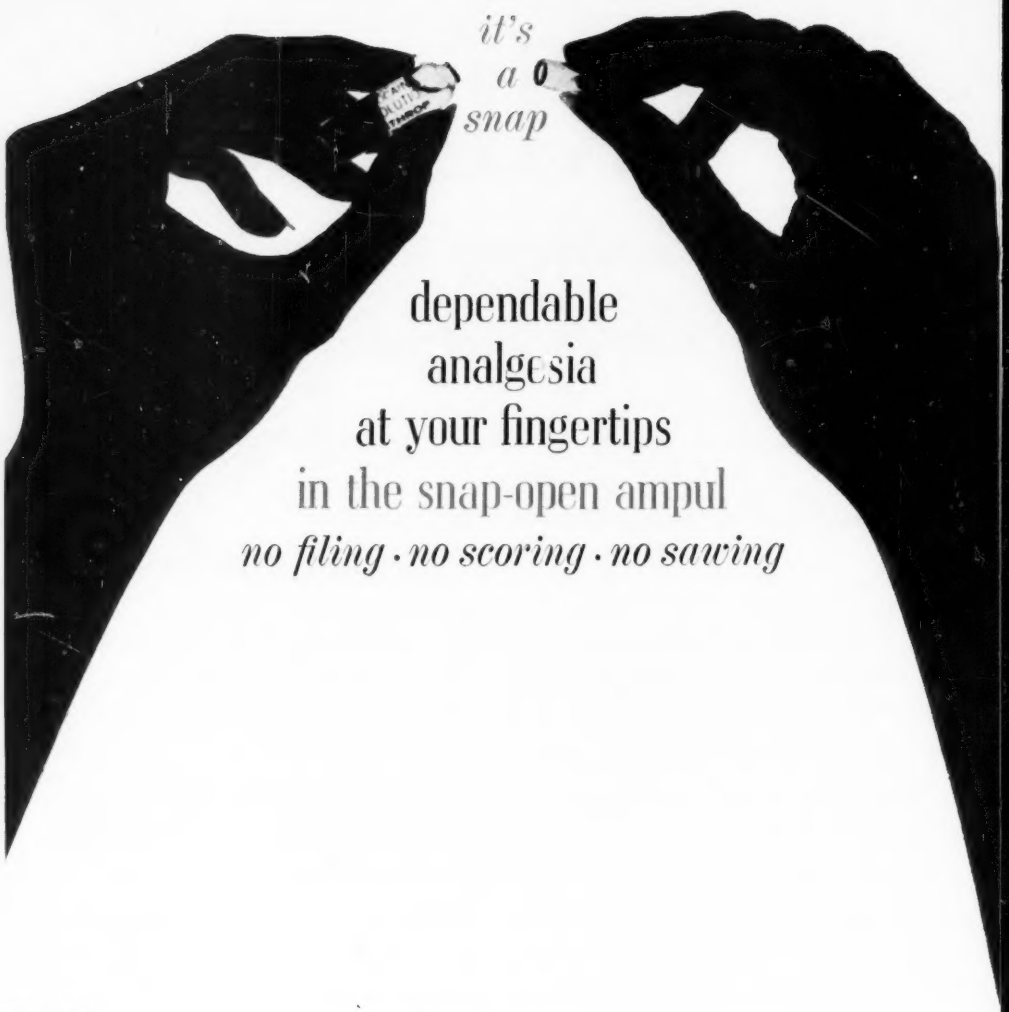
REFERENCE:
Knox, J. M., Everett, M. A., and Curtis, A. C.: New Uses For Surface-Active Agents. A.M.A. Arch. Derm. 74:699-706 (Dec. 1956)



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Authoritative new information that will help you better utilize griseofulvin for the benefit of your tinea patients will be made available to you by your Ayerst representative.

We trust that you will find it to your advantage to make griseofulvin available to your patients through your Rx for Griseofulvin Ayerst.

The average dosage of Griseofulvin Ayerst is one tablet q.i.d. or two tablets b.i.d. In more severe conditions, six to eight tablets daily (in divided doses) may be required initially.

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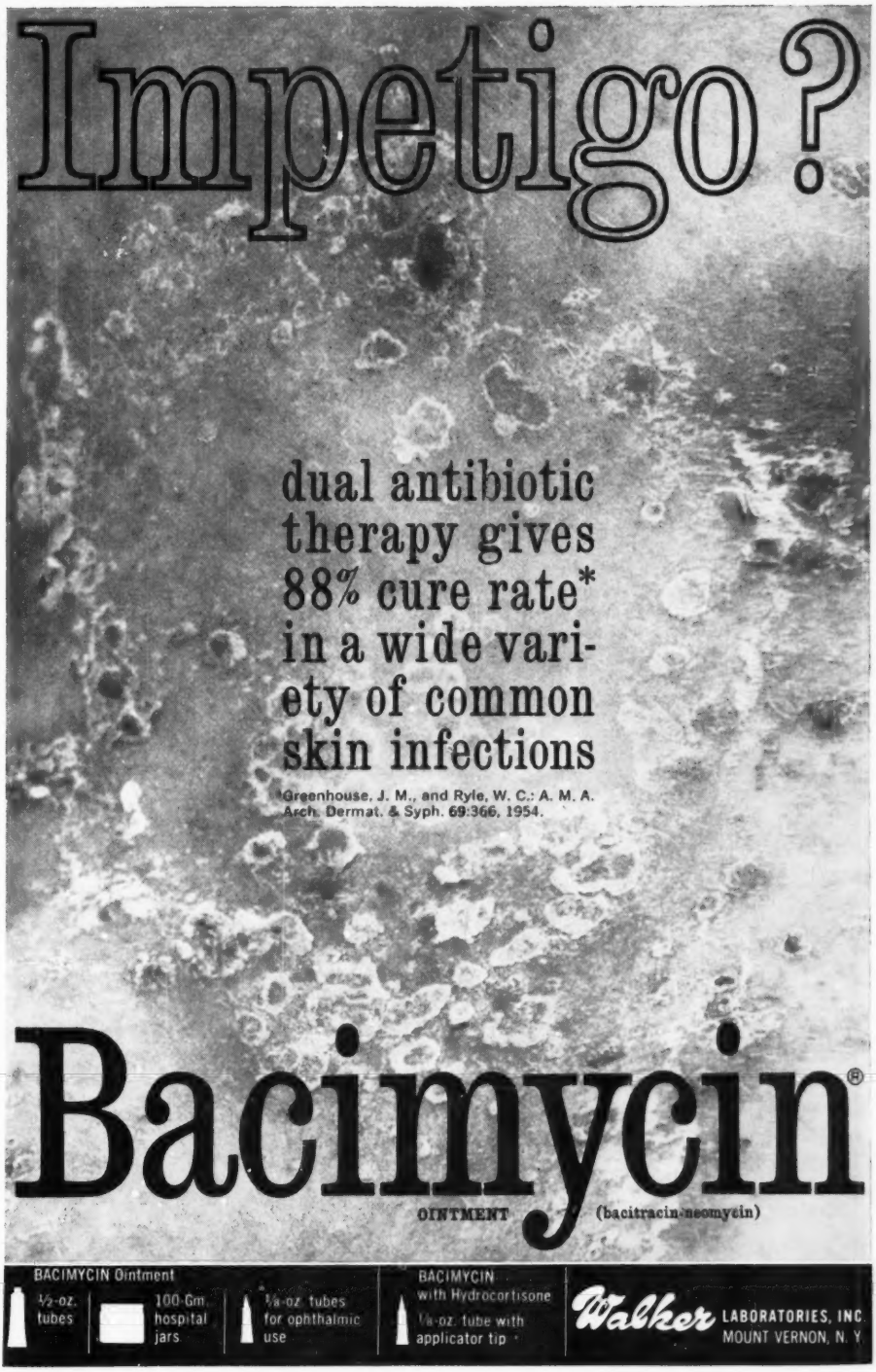
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